(12) UK Patent Application (19) GB (11) 2 351 081 (13) A

(43) Date of A Publication 20.12.2000

(21) Application No 9914222.6

(22) Date of Filing 18.06.1999

(71) Applicant(s)
Lilly Forschung Gmbh
(Incorporated in the Federal Republic of Germany)
Wiesingerweg 25, 20253 Hamburg,
Federal Republic of Germany

(72) Inventor(s)
Michael Paal
Gerd Ruehter
Theo Schotten
Wolfgang Stenzel

(74) Agent and/or Address for Service
C M Hudson
Erl Wood Manor, WINDLESHAM, Surrey, GU20 6PH,
United Kingdom

(51) INT CL[7]
C07D 233/06 , A61K 31/4164 31/42 , A61P 3/00 , C07D 263/10

(52) UK CL (Edition R)
C2C CAA CBK CKD CKF CKK CMM CNJ CNR CQN CRB CSF CTA CUL CWC CWD CWK CZB CZD CZL C1340 C1343 C1370 C1371 C139X C1396 C1412 C1416 C142X C1420 C1473 C1475 C1510 C1512 C1530 C1535 C200 C202 C213 C214 C215 C22Y C220 C222 C226 C246 C248 C25Y C250 C251 C252 C253 C254 C255 C256 C258 C28X C280 C281 C282 C29X C29Y C30Y C31Y C311 C313 C314 C32Y C321 C323 C326 C332 C337 C338 C34Y C341 C342 C35X C350 C351 C355 C36Y C360 C361 C362 C364 C365 C366 C367 C368 C37X C37Y C373 C385 C386 C396 C43X C464 C51X C510 C538 C54X C551 C578 C579 C584 C594 C601 C603 C61X C613 C62X C62Y C620 C621 C623 C624 C625 C626 C628 C634 C644 C65X C652 C658 C660 C661 C662 C665 C666 C668 C672 C69Y C694 C697 C699 C708 C71X C73Y C77X C77Y C774 C775 C776 C777 C778 C80Y C802
U1S S1317

(56) and (58) continued overleaf

(54) Abstract Title
Pharmaceutically active imidazoline compounds and analogues thereof

(57) Certain novel imidazoline compounds and analogues thereof are useful for the treatment of diabetes, diabetic complications, metabolic disorders, or related diseases where impaired glucose disposal is present.

GB 2 351 081 A

(56) Documents Cited
GB 2095663 A **WO 96/15126 A1** **WO 96/04241 A1**
WO 95/00468 A1 **US 5557002 A** **US 5210206 A**
Chemical Abstracts 127:185367 Chemical Abstracts 96:135352

(58) Field of Search
UK CL (Edition Q) **C2C**
INT CL[6] **C07D**
Online:CAS ONLINE

PHARMACEUTICAL COMPOUNDS

This invention relates to certain novel imidazoline-type compounds and analogues thereof, to their use for the treatment of diabetes, diabetic complications, metabolic disorders, or related diseases where impaired glucose disposal is present, to pharmaceutical compositions comprising them, and to processes for their preparation.

It is generally accepted that the control of blood glucose levels for the treatment of patients diagnosed with type II diabetes will have a beneficial effect. Established oral therapies for treating type II diabetes either improve insulin action or cause enhanced insulin secretion. Agents currently approved as therapies for type II diabetes patients that cause an enhanced insulin secretion contain a sulphonlyurea moiety. These compounds act by depolarising the beta cell by modulating closure of the K-ATP channel. Additional compounds that act at the K-ATP channel, which are not sulphonylureas compounds and which have a fast onset of activity and a short duration of action, are under consideration for treatment of type II diabetes. One such compound is (-)-N-(trans-4-isopropylcyclohexanecarbonyl)-D-phenylalanine (A-4166) (Brit. J. Pharm. 1997,120,137-145).

All agents that function at the molecular level by modulating the K-ATP channel have the potential for inducing hypoglycemia. Hypoglycemia is the major cause of adverse reactions in patients receiving sulphonylurea therapy and the prevalence of hypoglycemic episodes can be as high as 20% of patients. Compounds that potentiate insulin secretion under high glucose conditions and have little or no effect at low blood glucose levels would offer a distinct advantage in the treatment of type II diabetes.

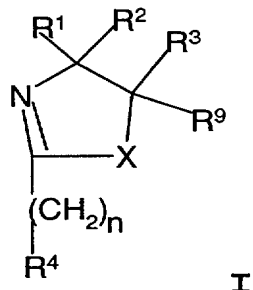
Compounds of the present invention potentiate the secretion of insulin from beta cells under high glucose conditions and have minimal effect under low glucose conditions.

The compounds are also operable in additional disease states where impaired glucose disposal is present. For example, these include cardiovascular disease where

above normal glucose levels are present or initial insulin resistance has occurred. The compounds can also be used to treat post operative insulin resistance induced by anaesthesia.

The present invention provides compounds of the following Formula (I), and the use of said compounds in the treatment of diabetes, especially Type II diabetes, diabetic complications, and metabolic disorders or related diseases in particular where impaired glucose disposal is present.

The present invention provides compounds of the following Formula (I):



I

wherein

R^1, R^2, R^3, and R^9 are each independently hydrogen or C_{1-8} alkyl; or

R^1 and R^3, together with the carbon atoms to which they are attached, combine to form a C_{3-7} carbocyclic ring and R^2 and R^9 are each independently hydrogen or C_{1-8} alkyl; or

R^1 and R^3, together optionally form a bond and R^2 and R^9 are each independently hydrogen or C_{1-8} alkyl; or

R^1 and R^2, together with the carbon atom to which they are attached combine to form a C_{3-7} spirocarbocyclic ring and R^3 and R^9 are each independently hydrogen or C_{1-8} alkyl; or

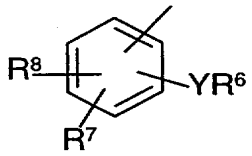
R^3 and R^9, together with the carbon atom to which they are attached, combine to form a C_{3-7} spirocarbocyclic ring and R^1 and R^2 are each independently hydrogen or C_{1-8} alkyl;

X is -O-, -S-, or $-NR^5-$;

R^5 is selected from the group consisting of hydrogen, C_{1-8} alkyl, optionally substituted aryl, and an amino protecting group;

n is 0, 1, or 2;

R^4 is a group of the formula:



Y is selected from the group consisting of a bond, $-O(CH_2)_k-$, $-(CH_2)_kO-$, -CO-, -CHOH-, -CONR-, -NRCO-, -NR'CONR''-, $-(CH_2)_kW(CH_2)_{R''''}-$, $-C\equiv C(CH_2)_k-$, $-(CH_2)_kC\equiv C-$, $-CH=CH(CH_2)_k-$, $-(CH_2)_kC=CH-$, NR'''', SO_2, SO_2NR'', and $NR'''SO_2$; wherein $-(CH_2)_kW(CH_2)_b-$ is optionally substituted with C alkyl or hydroxy;

k is independently 0, 1, 2, 3, or 4;

b is independently 0, 1, 2, 3, or 4;

provided that the sum of k and b together is not more than 4;

W is selected from the group consisting of a bond, O, S, SO_2, SO, SO_2NR'', NR'' SO_2, NR'', CONR', NR'CO, -C=C-, -C≡C-, C=O, and $NR''''CONR''''$;

R, R', R'' and R''' are each independently selected from the group consisting of hydrogen, C_{1-4} alkyl, and benzyl;

R'''' is selected from the group consisting of of hydrogen, C_{1-8} alkyl, benzyl, and an amino protecting group;

R^8 is selected from the group consisting of hydrogen, C_{1-8} alkyl, C_{1-8} alkoxy, C_{3-7} cycloalkyl, C_{3-7} cyclo C_{1-8} alkoxy, hydroxy, halo, carbo C_{1-8} alkoxy, halo C_{1-6} alkyl, halo-C_{1-8} alkoxy, optionally substituted phenyl C_{1-8} alkyl;

R^7 is selected from the group consisting of hydrogen, C_{1-8} alkyl, C_{1-8} alkoxy, C_{3-7} cycloalkyl, C_{3-7} cyclo C_{1-8} alkoxy, hydroxy, halo, carbo C_{1-8} alkoxy, halo C_{1-6} alkyl, halo-C_{1-8} alkoxy, optionally substituted phenyl C_{1-8} alkyl, optionally substituted phenyloxy, optionally substituted phenyl C_{1-8} alkoxy, optionally substituted naphthyl, optionally substituted heteroaryl, (tetrahydropyran-2-yl)methoxy, C_{1-8} alkyl-$S(O)_m$, optionally substituted aryl-C_{1-8} alkyl-$S(O)_{m'}$, $CH_3(CH_2)_p$-Z^1-$(CH_2)_q$-Z^2-, and Z^3-$(CH_2)q'$-Z^2-;

where

Z^1 and Z^2 are each independently a bond, -O-, -S-,  , SO_2, sulphoximino, or NR^{13};

Z^3 is hydroxy, protected hydroxy, $NR^{14}R^{15}$, protected amino, SH, or protected SH;

R^6 is selected from the group consisting of optionally substituted phenyl, optionally substituted naphthyl, optionally substituted heteroaryl, and optionally substituted 4,5-dihydroisoxazolinyl;

R^{13}, R^{14} and R^{15} are each independently selected from the group consisting of hydrogen, C_{1-8} alkyl, optionally substituted aryl C_{1-8} alkyl, and optionally substituted phenyl; or R^{14} and R^{15} together with the nitrogen atom to which they are attached may combine to form a heterocyclic ring comprising the nitrogen and C_{2-6} alkyl, wherein C_{2-6}alkyl is optionally substituted with one or two C_{1-8} alkyl groups or one carbon atom of the heterocyclic ring is optionally replaced by oxygen or sulfur;

p is 0, 1, 2, 3, or 4;

q and q' are each independently selected from the group consisting of 1, 2, 3, 4, and 5;

m and m' are each independently selected from the group consisting of 0, 1 and 2; and

pharmaceutically acceptable salts and esters thereof.

One embodiment of the present application is the use of a compound of the Formula I or a pharmaceutically acceptable salt or ester thereof, in the manufacture of a medicament for treating diabetes or a related disorder.

Another embodiment of the present invention is a method of treating diabetes or a related disorder, which comprises administering to a patient a compound of Formula I, or a pharmaceutically acceptable salt thereof.

In the above formulae, a "C_{1-8} alkyl" group can be any alkyl group, branched or unbranched, containing up to eight carbon atoms, likewise, $C_{1-n'}$ alkyl is a branched or unbranched alkyl containing up to n' carbon atoms whereing n' is an integer. Examples include methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tertiary butyl, pentyl and hexyl. Preferred values of C_{1-8} alkyl are C_{1-6} alkyl, and most preferably methyl and ethyl.

The term "C_{1-8} alkylthio" has the meaning known to the artisan. That is that one of the carbon atoms is replaced with a sulfur atom.

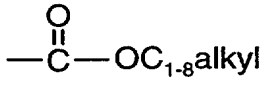
A "C_{3-7} cycloalkyl" group is a saturated carbon ring having from 3 to 7 carbon atoms. Such groups include, but are not limited to, as cyclopropyl, cyclobutyl, cycloheptyl, cyclohexyl or cyclopentyl.

A "C_{3-7} cycloalkyl-C_{1-8} alkyl" group is one such cycloalkyl group attached through a C_{1-8} alkyl group to the cycloalkyl group. It is especially preferred that the alkyl group is C_{1-6} alkyl.

A "C_{1-8} alkoxy" group is one of the above-mentioned C_{1-8} alkyl groups attached through oxygen to the base molecule, and preferred examples are methoxy and ethoxy.

A "C_{3-7} cycloalkoxy" group is a C_{3-7} cycloalkyl group as mentioned above linked through an oxygen atom to the cycloalkyl as, for example, cyclopropyloxy, cyclopentyloxy and cyclohexyloxy.

A "C_{3-7} cycloalkylC_{1-8} alkoxy" group is a C_{3-7} cycoalkyl-C_{1-8} alkyl as mentioned above linked through an oxygen atom to the base molecule as, for example, cyclohexylmethoxy.

A "carbo(C_{1-8})alkoxy" group is a  group, for example a carbomethoxy or carboethoxy group.

An "optionally substituted aryl" group is a mononuclear or polynuclear aromatic hydrocarbon group, for example phenyl or naphthyl, which is optionally substituted with from one to three substituents each independently selected from the group consisting of C_{1-8} alkyl, C_{1-8} alkoxy, carboxy, hydroxy, cyano, halo, trifluoromethyl, SCH_3, nitro, phenyl, 3,4-methylenedioxy, amino, and phenyl which is optionally substituted by from one to three substituents independently selected from the group consisting of C_{1-8} alkyl, C_{2-8} alkenyl, C_{1-8} alkoxy, alkoxyhydroxymethyl, alkoxy hydroxyformyl, C_{1-8} alkoxy, carboxy, hydroxy, cyano, halo, trifluoromethyl, SCH_3, nitro, phenyl, 3,4-methylenedioxy, and amino., carboxy, hydroxy,

An "optionally substituted 4,5-dihydroisoxazolinyl" means a dihydroisoxazolinyl group which is optionally substituted with from one to three substituents selected from the group consisting of C_{1-8} alkyl, C_{2-8} alkenyl, C_{1-8} alkoxy, alkoxyhydroxymethyl, alkoxy hydroxyformyl, C_{1-8} alkoxy, carboxy, hydroxy, cyano, halo, trifluoromethyl, SCH_3, nitro, phenyl, 3,4-methylenedioxy, and amino.

An "optionally substituted phenyl" group is a phenyl which is optionally substituted with from one to three substituents independently selected from the group consisting of C_{1-8} alkyl, C_{1-8} alkoxy, carboxy, hydroxy, cyano, halo, trifluoromethyl, SCH_3, nitro, phenyl, 3,4-methylenedioxy, amino, and phenyl which is optionally substituted by from one to three substituents independently selected from the group consisting of C_{1-8} alkyl, C_{2-8} alkenyl, C_{1-8} alkoxy, alkoxyhydroxymethyl, alkoxy hydroxyformyl, C_{1-8} alkoxy, carboxy, hydroxy, cyano, halo, trifluoromethyl, SCH_3, nitro, phenyl, 3,4-methylenedioxy, and amino.

An "optionally substituted naphthyl" group is a naphthyl which is optionally substituted with from one to three substituents independently selected from, the group consisting of C_{1-8} alkyl, C_{1-8} alkoxy, carboxy, hydroxy, cyano, halo, trifluoromethyl, SCH_3, nitro, phenyl, 3,4-methylenedioxy, amino, and phenyl which is optionally substituted by from one to three independently selected from the group consisting of C_{1-8} alkyl, C_{1-8} alkoxy, carboxy, hydroxy, cyano, halo, trifluoromethyl, SCH_3, nitro, phenyl, 3,4-methylenedioxy, and amino.

An "optionally substituted COaryl" group is an optionally substituted aryl which is bound to the base molecule through a group of the formula:  . The optionally substituted aryl group is defined herein above.

A "optionally substituted aryl-C_{1-8} alkyl-$S(O)_{m}$·· " group is an optionally substituted aryl which is bound to the base molecule through an alkyl-$S(O)_{m}$·· group, wherein the S- bonds to the base molecule. The optionally substituted aryl group is as defined herein above.

"Heteroaryl" means a four to a ten membered aromatic mononuclear, binuclear or trinuclear ring system in which from one to three atoms of the ring system are each

independently selected from the group consisting of nitrogen, oxygen, and sulfur. Examples of heteroaryl groups include, but are not limited to, naphthofuran, imidazo [1,2-a] pyridyl, imidazo [1,2-a] pyrimidyl, imidazo [1,2-b] pyrazinyl, imidazo [1,2-b] pyrazinyl, imidazo [2,1-b] thiazolinyl, imidazo [1,2-b] benzothiazolinyl, imidazo [1,2-b] benzoxazolinyl, 1H- imidazo [1,2-a] benzimidazolinyl, indolyl, imidazolyl, furanyl, thienyl, isoquinolinyl, benzofuranyl, benzothienyl, pyridyl, quinolinyl, oxazolyl, pyrrolyl, isoxazolyl, pyrimidyl, thiazolyl, and benzimidazolyl. An "optionally substituted heteroaryl" group is a heteroaryl group which is optionally substituted with from one to three substituents each independently selected from the group consisting of C_{1-8} alkyl, C_{1-8} alkoxy, carboxy, alkoxy carbonyl, formyl, hydroxy, cyano, halo, trifluoromethyl, SCH_3, nitro, phenyl, 3,4-methylenedioxy, amino, and phenyl which is optionally substituted by from one to three substituents each independently selected from the group consisting of C_{1-8} alkyl, C_{1-8} alkoxy, carboxy, hydroxy, cyano, halo, trifluoromethyl, SCH_3, nitro, phenyl, 3,4-methylenedioxy, and amino.

"Optionally substituted heterocyclyl" means a four to 10 membered mononuclear or binuclear saturated or partially unsaturated ring system in which from one to three atoms of the ring system are each independently selected from the group consisting of nitrogen, oxygen, and sulfur, and which ring system is optionally substituted with from one to three substituents each independently selected from the group consisting of C_{1-8} alkyl, C_{1-8} alkoxy, carboxy, hydroxy, cyano, halo, trifluoromethyl, SCH_3, nitro, phenyl, 3,4-methylenedioxy, amino, and phenyl which is optionally substituted by from one to three substituents each independently selected from the group consisting of C_{1-8} alkyl, C_{1-8} alkoxy, carboxy, hydroxy, cyano, halo, trifluoromethyl, SCH_3, nitro, phenyl, 3,4-methylenedioxy, and amino. Examples of heterocyclyl groups include, but are not limited to, piperidinyl, piperazinyl, imidazolidinyl, tetrahydrofuranyl, morpholinyl, homopiperidinyl, tetrahydroquinolinyl, dioxanyl, and tetrahydropyranyl.

An "aryl-C_{1-8} alkyl" group can be, for example, optionally substituted phenyl-C_{1-8} alkyl or optionally substituted naphthyl-C_{1-8} alkyl, such optionally substituted phenyl or naphthyl groups being optionally substituted with one or more, preferably

one to three, substituents selected from, C_{1-8} alkyl, C_{1-8} alkoxy, carboxy, hydroxy, cyano, halo, trifluoromethyl, SCH_3, nitro and amino. A preferred aryl-C_{1-8} alkyl group is optionally substituted phenyl-$(CH_2)_x$- where x is 1 or 2, most preferably optionally substituted benzyl. Thus, the alkyl group serves as the link between the phenyl or naphtyl and the base molecule.

An "optionally substituted phenyloxy" is a group wherein the phenyl group is attached to the base molecule through an oxygen, and such phenyl group is optionally substituted with one or more, preferably one to three, substituents selected from, C_{1-8} alkyl, C_{1-8} alkoxy, carboxy, hydroxy, cyano, halo, trifluoromethyl, SCH_3, nitro and amino.

An "optionally substituted phenylC_{1-8} alkoxy" is a group wherein the phenyl group is attached to the base molecule through an alkoxy group, and such phenyl group is optionally substituted with one or more, preferably one to three, substituents selected from, C_{1-8} alkyl, C_{1-8} alkoxy, carboxy, hydroxy, cyano, halo, trifluoromethyl, SCH_3, nitro and amino.

Of course, it will be understood that "optionally substituted" means that there may be zero non-hydrogen substituents.

An "aryl-C_{1-8} alkoxy" group can be, for example, optionally substituted phenyl-C_{1-8} alkoxy or optionally substituted naphthyl-C_{1-8} alkoxy, such optionally substituted groups being optionally substituted with one or more, preferably one to three, substituents selected from, for example, C_{1-8} alkyl, C_{1-8} alkoxy, carboxy, hydroxy, cyano, halo, trifluoromethyl, SCH_3, nitro and amino. A preferred aryl-C_{1-8} alkyl group is optionally substituted phenyl-$(CH_2)_x$- where x^- is 1 or 2. Thus, the aryl is linked to the base molecule through the alkoxy group.

A halo group is preferably chloro, bromo or fluoro.

A "halo C_{1-8} alkyl" or "halo C_{1-8} alkoxy" or "halo C_{1-8} alkylthio" is a substituent in which one or more, preferably one to three, hydrogen atoms on the C_{1-8} alkyl moiety is replaced by a halo atom, preferably chloro, bromo or fluoro. Trifluoromethyl is one preferred haloalkyl group.

An "alkoxyalkoxy" group is of the formula $CH_3(CH_2)_p$-O-$(CH_2)_q$-O-, where p is 0-4 and q is 1-5, preferred examples being those in which p is 0 or 1 and q is 1-3, especially methoxyethoxy, ethoxyethoxy, ethoxypropoxy, or methoxypropoxy.

The term "spirocarbocyclic" means a ring which is fused to the base molecule through one shared tetravalent carbon atom to form two rings which are annelated by a single carbon atom.

The "acyl" moiety, alone or in combination, is derived from an alkanoic acid containing from one to eight carbon atoms. The term "acyl" also includes moieties derived from an aryl carboxylic acid or heteroaryl.

As used herein, the term "aryl coupling" shall mean any appropriate method for coupling two aromatic or heteroaromatic rings known to the artisan. Such methods may include, but are not limited to Ullmann, Stille coupling or Suzuki coupling methods. The Suzuki coupling is an especially preferred coupling method. The Suzuki method using aryl boronic acid derivatives, e.g. Ar-$B(OH)_2$ and Pd catalyst is particularly preferred for use in the synthesis methods described herein. The artisan will appreciate that there are a variety of available Pd catalysts which are acceptable for the Suzuki coupling. One such Pd catalyst which is preferred for the methods described herein is $Pd(PPh_3)_4$.

The artisan will also appreciate that there are a variety of available metal catalysts other than Pd which are acceptable for aryl coupling reactions.

The term "base molecule" means the ring system to which the named substituent is bound.

The term "treating", as used herein, describes the management and care of a patient for the purpose of combating the disease, condition, or disorder and includes the administration of a compound of present invention to prevent the onset of the symptoms or complications, to alleviate the symptoms or complications, or to eliminate the disease, condition, or disorder.

As used herein the term "amino protecting group" means any of the conventional amino protecting groups, see, for instance, T. W. Greene, Protective Groups in Organic Synthesis, chapter 7, John Wiley and Sons, New York, 1981, and

by J. W. Barton, Protective Groups in Organic Chemistry, chapter 2, J. F. W. McOmie, ed., Plenum Press, New York, 1973. Examples of such groups include but are not intended to be limited to benzyl and substituted benzyl such as 3,4-dimethoxybenzyl, o-nitrobenzyl, and triphenylmethyl; those of the formula -COOR where R includes such groups as methyl, ethyl, propyl, isopropyl, 2,2,2-trichloroethyl, 1-methyl-1-phenylethyl, isobutyl, t-butyl, t-amyl, vinyl, allyl, phenyl, benzyl, p-nitrobenzyl, o-nitrobenzyl, and 2,4-dichlorobenzyl; acyl groups and substituted acyl such as formyl, acetyl, chloroacetyl, dichloroacetyl, trichloroacetyl, trifluoroacetyl, benzoyl, and p-methoxybenzoyl; and other groups such as methanesulfonyl, p-toluenesulfonyl, p-bromobenzenesulfonyl, p-nitrophenylethyl, p-toluenesulfonylaminocarbonyl, and the like. Preferred nitrogen protecting groups are benzyl, acyl, like benzyloxycarbonyl or t-butyloxycarbonyl, or silyl or acetyl phenyloxycarbonyl.

The term "protected amino" means that the amino group is substituted with an amino protecting group, as defined herein.

As used herein the term "protected hydroxy" means that the hydroxyl group is substituted with any of the conventional hydroxyl protecting groups, see, for instance, T. W. Greene, Protective Groups in Organic Synthesis, chapter 2, John Wiley and Sons, New York, 1981, and by J. W. Barton, Protective Groups in Organic Chemistry, J. F. W. McOmie, ed., Plenum Press, New York, 1973. Examples of such groups include but are not intended to be limited to acetals, ethers such as silyl ethers and the like; esters such as formate, benzoylformate, acetate, phenoxyacetate and the like; carbonates such as methyl carbonate, ethyl carbonate, isobutylcarbonate, benzyl, nitrobenzyl, and the like; and others such as nitrate, borate, phenylcarbamate, tetrahydropyrinyl (THP), trityloxypyrinyl and the like. The artisan will recognise that the art includes other acceptable protecting groups as provided by the cited references.

As used herein the term "protected SH" means that the thiol group is substituted with any of the conventional thiol protecting groups, see, for instance, T. W. Greene, Protective Groups in Organic Synthesis, chapter 6, John Wiley and Sons, New York, 1981, and by J. W. Barton, Protective Groups in Organic Chemistry, J. F. W. McOmie, ed., Plenum Press, New York, 1973. Examples of such groups

include but are not intended to be limited to thioethers like benzylthioether, 4-methylbenzylthioether, p-nitrobenzylthioether, diphenylmethylthioether, substituted methyl derivatives such as methoxymethyl (MOM), isobutoxymethyl, 2-tetrahydropyranyl, thioesters like, acetyl, benzoyl, thiocarbonates like t-butoxycarbonyl, and the like.

The compounds of the present invention can be useful for modulating insulin secretion and as research tools. Certain compounds and conditions within the scope of this invention are preferred. The following conditions, invention embodiments, and compound characteristics listed in tabular form may be independently combined to produce a variety of preferred compounds and process conditions. The following list of embodiments of this invention is not intended to limit the scope of this invention in any way. Some prefered characteristics of compounds of Formula **I** are:

(i) R^1 and R^2 are hydrogen and R^3 and R^9 are each hydrogen or methyl;

(ii) R^1, R^2, R^3 and R^9 are each hydrogen;

(iii) X is NH;

Y is selected from the group consisting of $-O(CH_2)_k-$, $-(CH_2)_kO-$, -CO-,

(vi) -CHOH-, -CONR-, -NRCO-, -NR'CONR''-,

$-(CH_2)_kW(CH_2)_{R''''}-$, $-C\equiv C(CH_2)_k-$, $-(CH_2)_kC\equiv C-$,

$-CH=CH(CH_2)_k-$, $-(CH_2)_kC=CH-$, NR'''', SO_2, SO_2NR'',

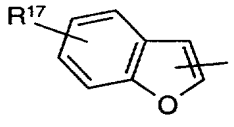
and $NR'''SO_2$;

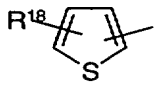
(vii) Y is $-(CH_2)_kW(CH_2)_{R''''}-$;

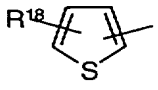
(viii) Y is selected from the group consisting of -C=C-, $-C\equiv C(CH_2)_k-$,

$-(CH_2)_kC\equiv C-$, $-CH_2C=C(CH_2)_k-$, and $-(CH_2)_kC=CCH_2-$;

(ix) Y is a bond;

(x) R^6 is heteroaryl wherein heteroaryl is  R^{17} is substituted phenyl, halo, naphthyl, or a group of

the formula:  where R^{18} is halo, hydrogen, $-C_{1-3}$alkoxy;

(xi) R^6 is heteroaryl wherein heteroaryl is  where R^{18} is halo, hydrogen, $-C_{1-3}$alkoxy;

(xii) n is 1;

(xiii) R^6 is substituted phenyl where the phenyl ring is substituted with up to three substituents selected from the group consisting of halo, naphthyl, halo C_{1-6} alkyl, C_{1-6} alkoxy, NO_2, and C_{1-6} alkyl;

(xiv) R^7 is selected from the group consisting of halo, nitro, cyano, C_{2-6} alkyl, halo C_{1-6} alkyl, halo C_{1-6} alkoxy, or halo C_{1-6} alkylthio;

(xv) n is 0;

(xvi) X is O or S;

(xvii) R^7 is selected from the group consisting of halo, C_{2-6} alkyl, and halo C_{1-6} alkyl;

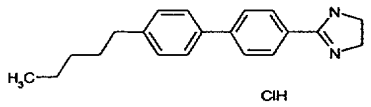
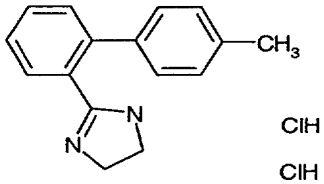
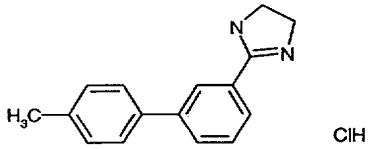
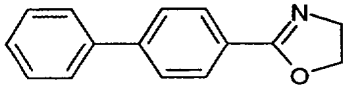
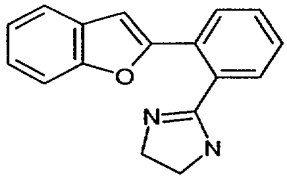
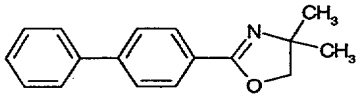
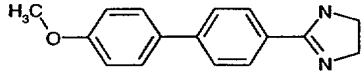
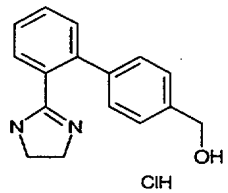
(xviii) R^6 is 3-chlorobenzyl, phenyl, 4-methylphenyl, 2,4-dichlorophenyl, 3-methyl-2-thienyl, 2,5-dimethyl-3-thienyl, 4-methoxyphenyl, 2-methoxyphenyl, 4-chlorophenyl, 3-chlorophenyl, 2-chlorophenyl, 2-methylphenyl, 3-methylphenyl, 3-thienyl, 2-bromophenyl, 4-chloro-3-methylphenyl, 2,4-dimethylphenyl, 2-(trifluoromethyl)phenyl, and 3-fluorophenyl;

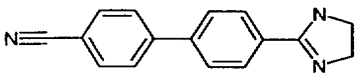
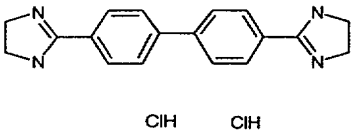
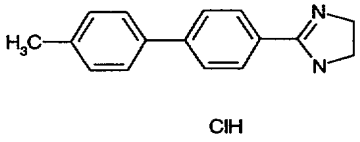
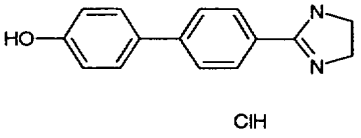
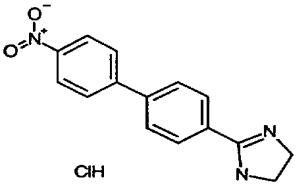
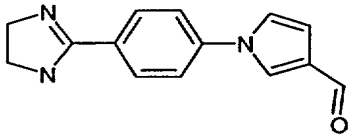
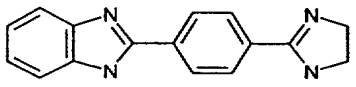
(xix) Y is not a bond;

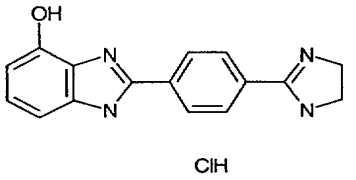
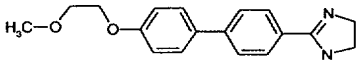
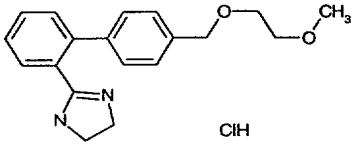
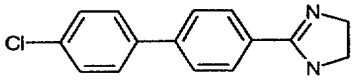
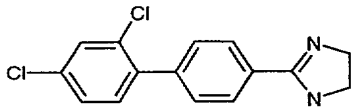
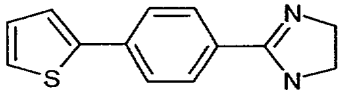
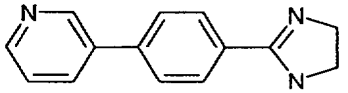
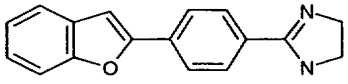
(xx) R^6 is optionally substituted naphthyl;

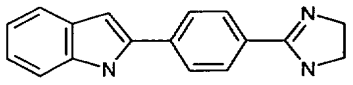
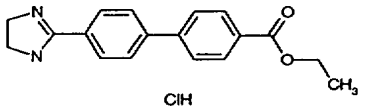
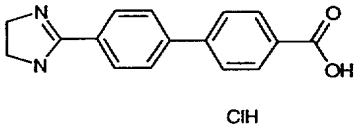
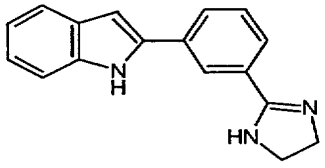
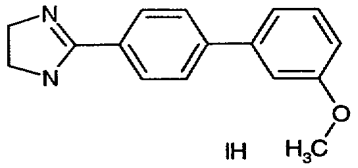
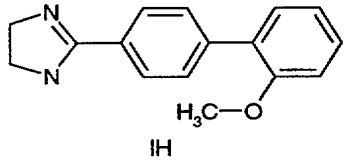
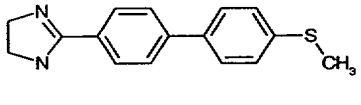
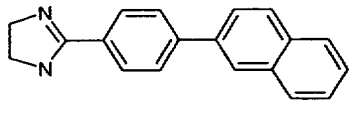
(xxi) R^1 and R^3 together form a bond;

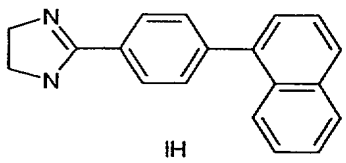
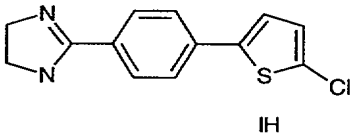
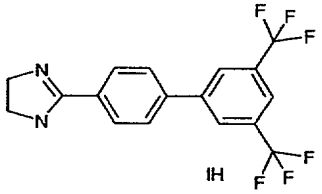
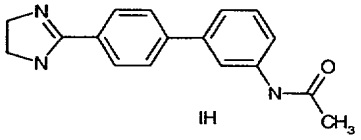
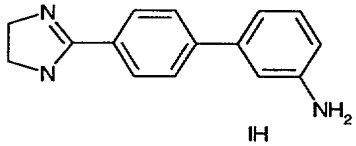
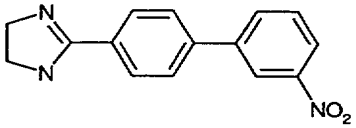
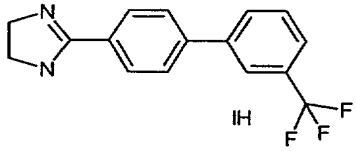
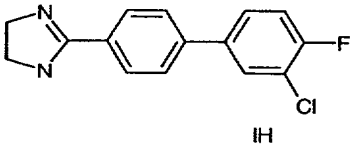
(xxii) Preferred compounds of this invention include any one of the following compounds:

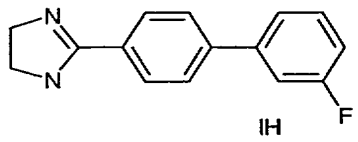
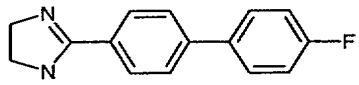
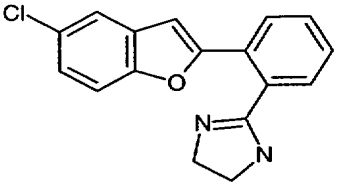
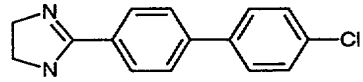
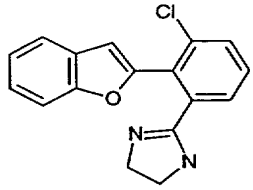
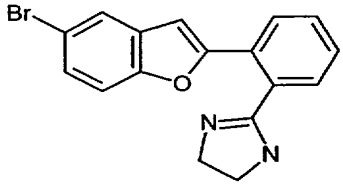
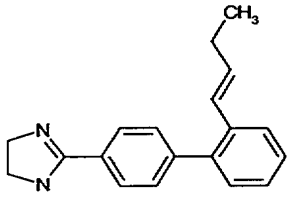
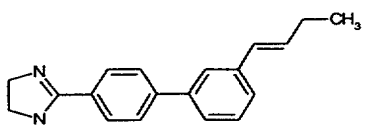
1	
2	
3	
4	
5	
6	
7	
8	

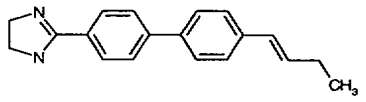
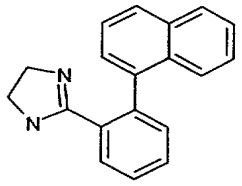
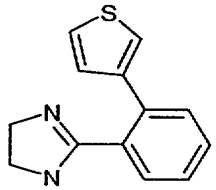
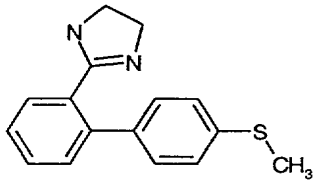
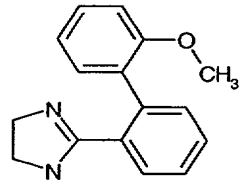
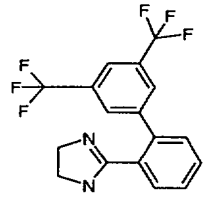
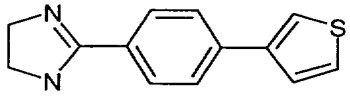
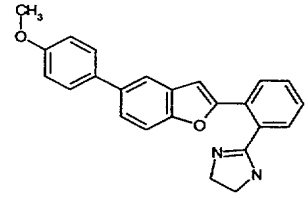
9	
10	
11	
12	
13	
14	
15	
16	

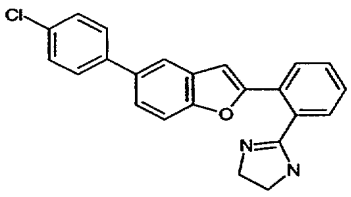
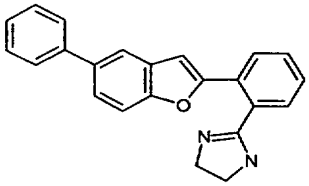
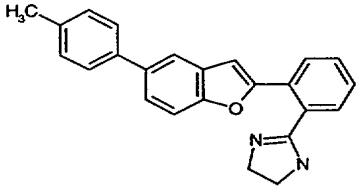
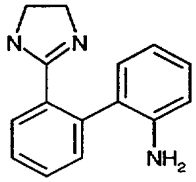
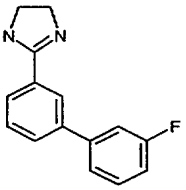
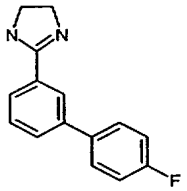
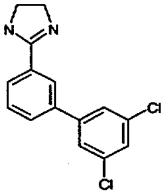
17	 ClH
18	
19	 ClH
20	 ClH
21	
22	
23	
24	

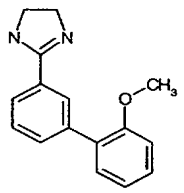
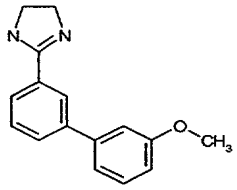
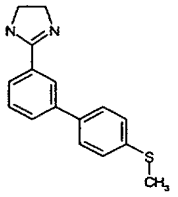
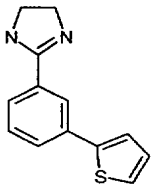
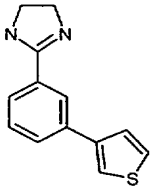
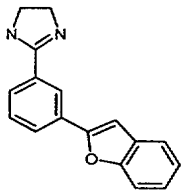
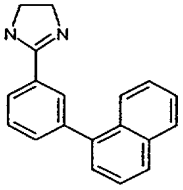
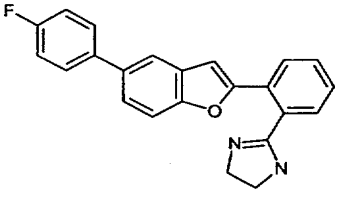
25	
26	 ClH
27	 ClH
28	
29	 IH
30	 IH
31	 IH
32	 IH

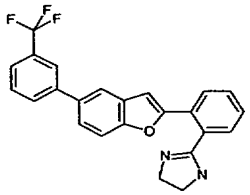
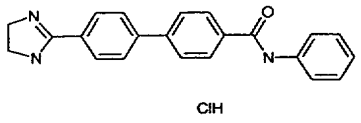
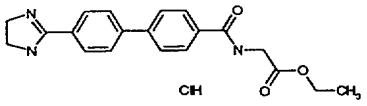
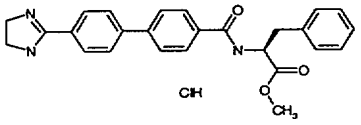
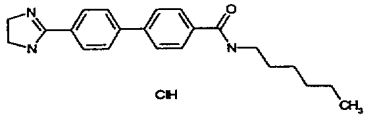
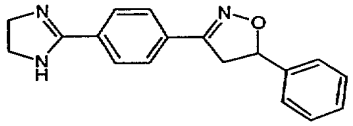
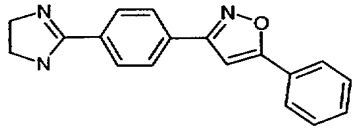
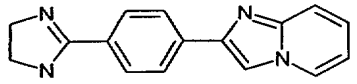
33	
34	
35	
36	
37	
38	
39	
40	

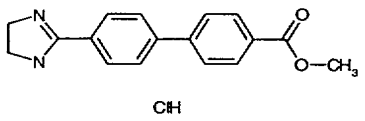
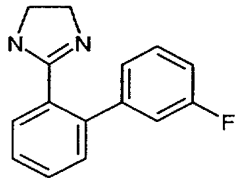
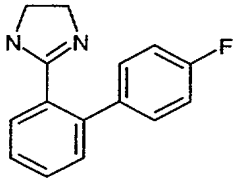
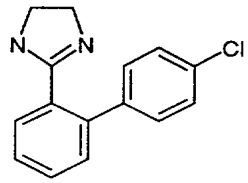
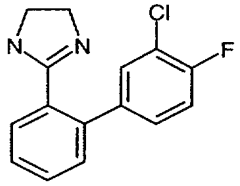
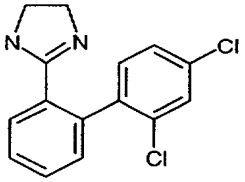
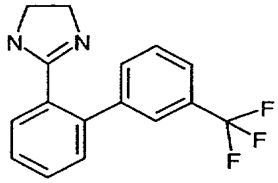
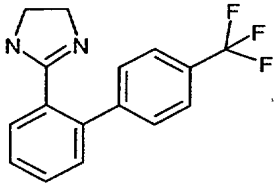
41	 IH
42	
43	
44	 IH
45	
46	
47	
48	

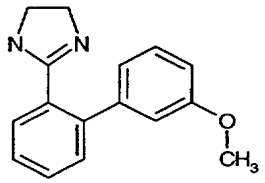
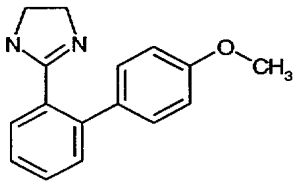
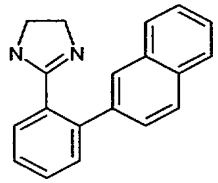
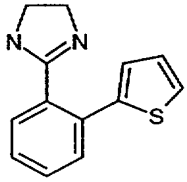
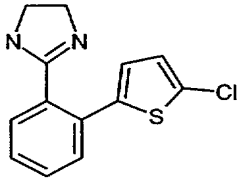
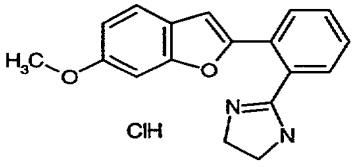
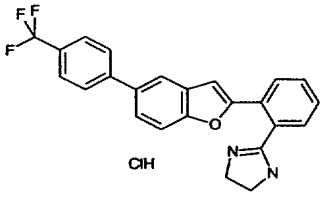
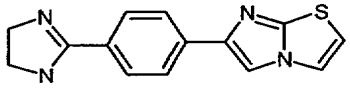
49	
50	
51	
52	
53	
54	
55	
56	

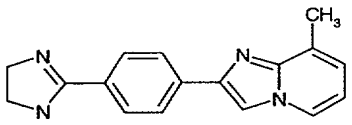
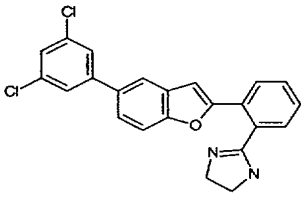
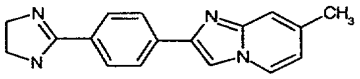
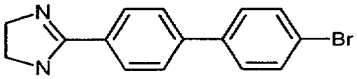
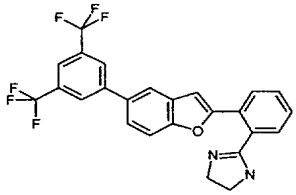
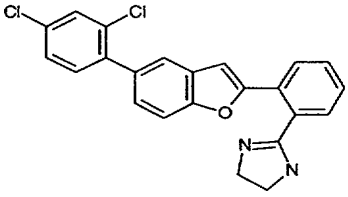
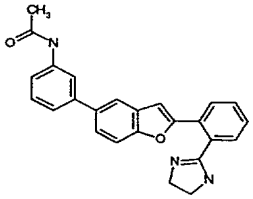
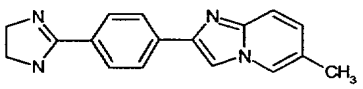
57	
58	
59	
60	
61	
62	
63	
64	

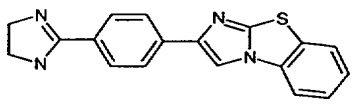
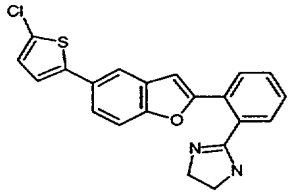
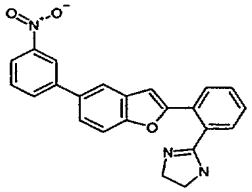
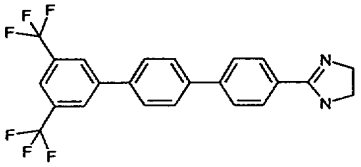
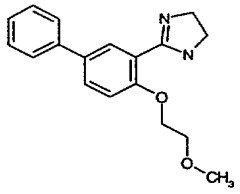
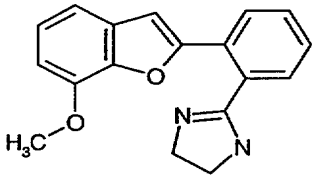
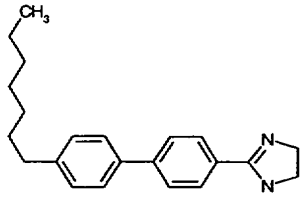
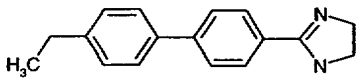
65	
66	
67	
68	
69	
70	
71	
72	

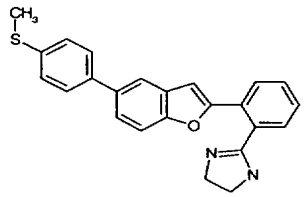
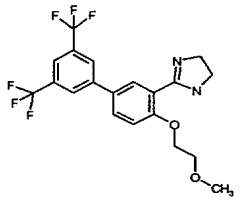
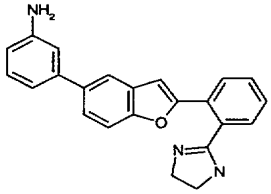
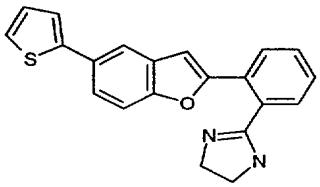
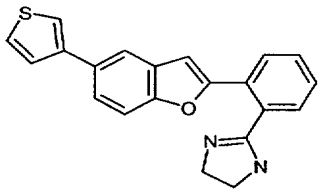
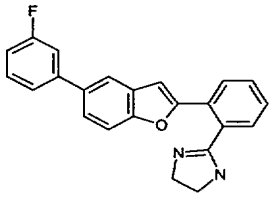
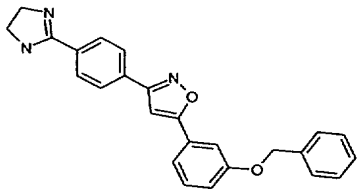
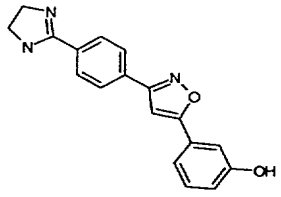
73	
74	
75	
76	
77	
78	
79	
80	

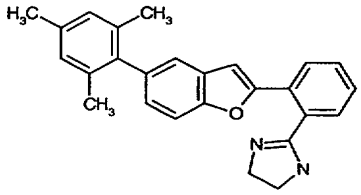
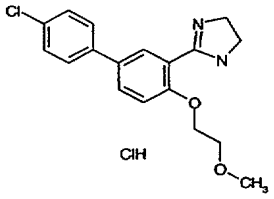
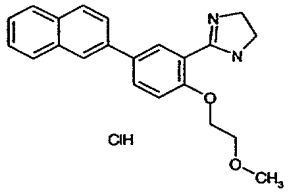
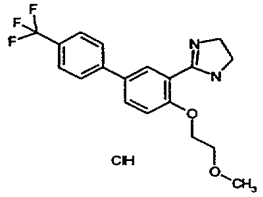
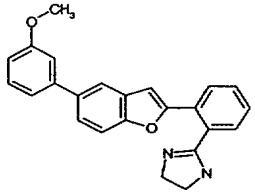
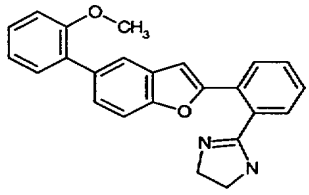
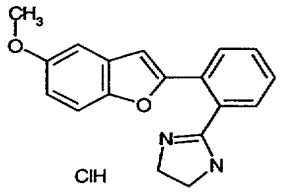
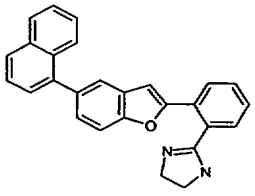
81	
82	
83	
84	
85	
86	
87	
88	

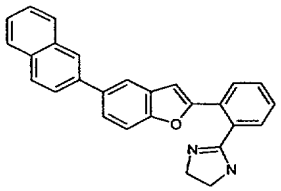
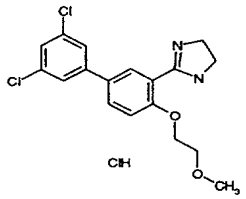
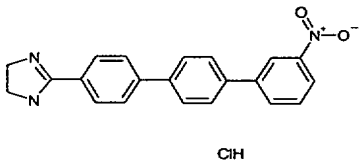
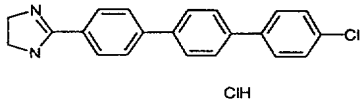
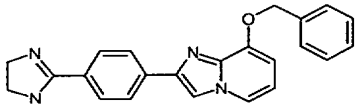
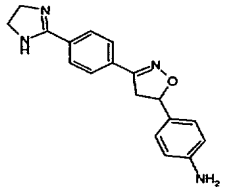
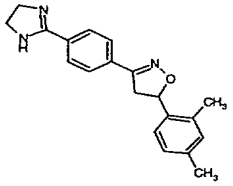
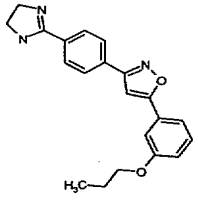
89	
90	
91	
92	
93	
94	
95	
96	

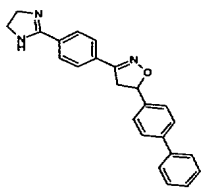
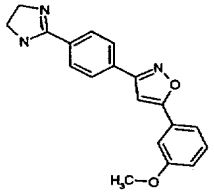
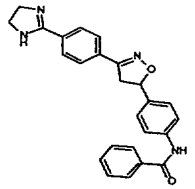
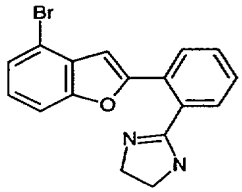
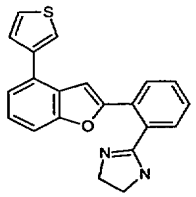
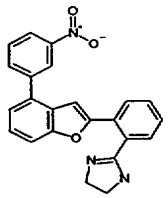
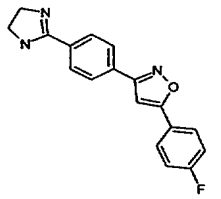
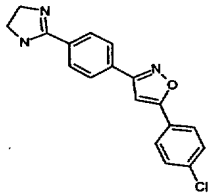
97	
98	
99	
100	
101	
102	
103	
104	

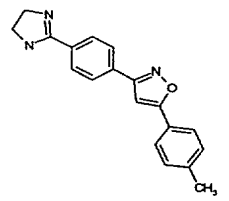
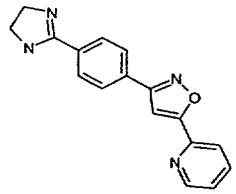
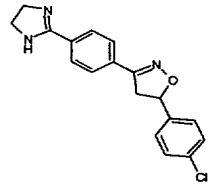
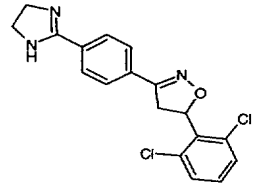
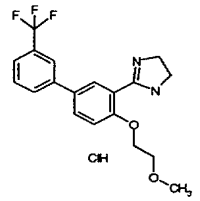
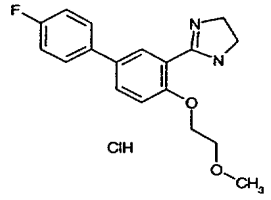
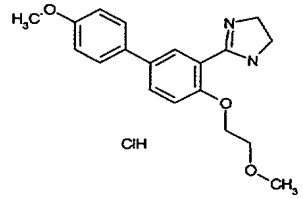
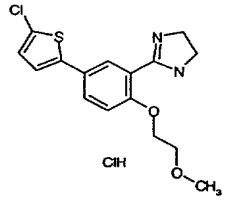
105	
106	
107	
108	
109	
110	
111	
112	

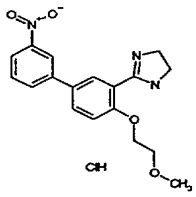
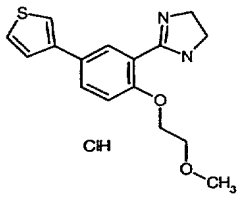
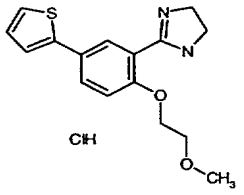
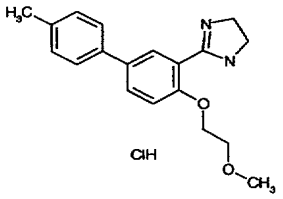
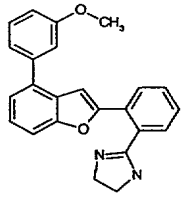
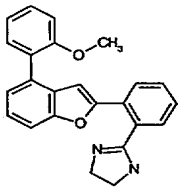
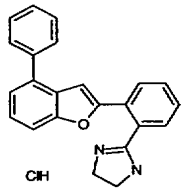
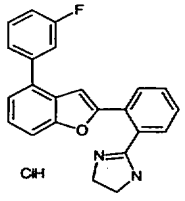
113	
114	
115	
116	
117	
118	
119	
120	

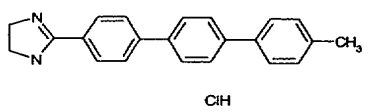
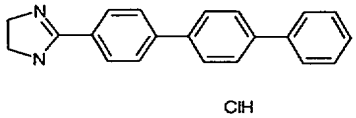
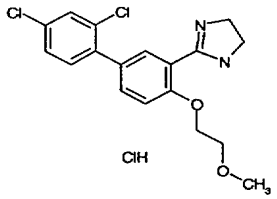
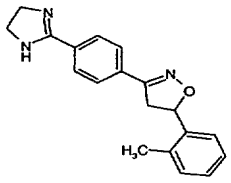
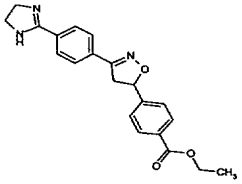
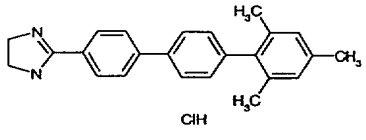
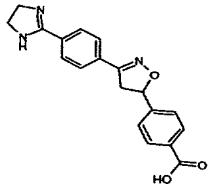
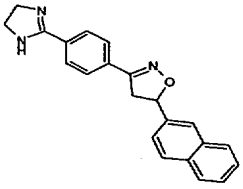
121	
122	
123	
124	
125	
126	
127	
128	

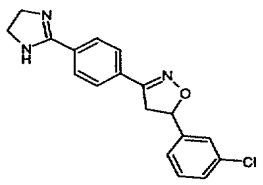
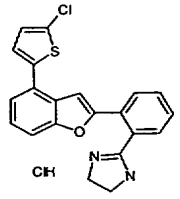
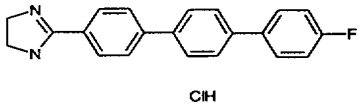
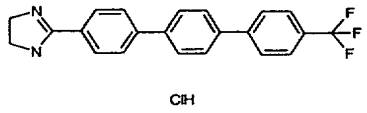
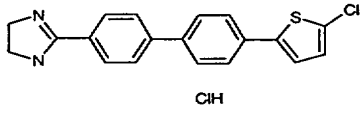
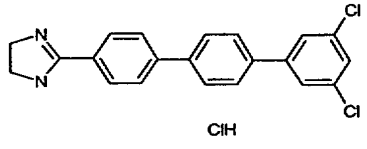
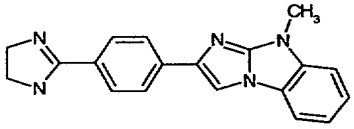
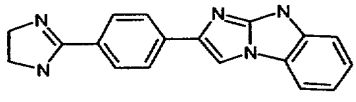
129	
130	
131	
132	
133	
134	
135	
136	

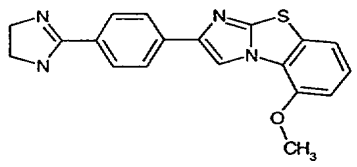
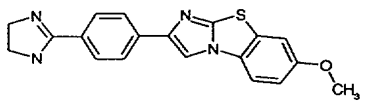
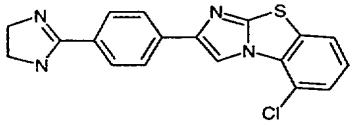
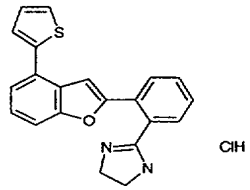
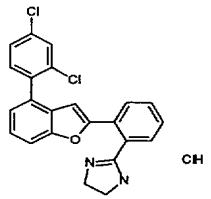
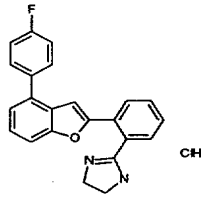
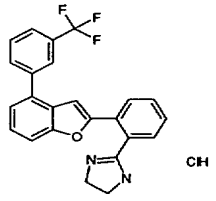
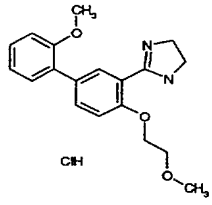
137	
138	
139	
140	
141	
142	
143	
144	

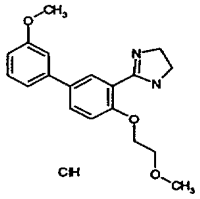
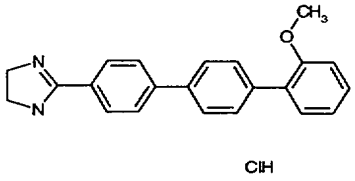
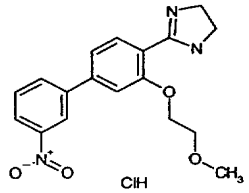
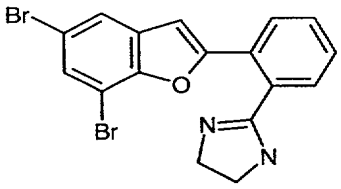
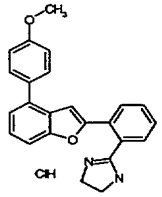
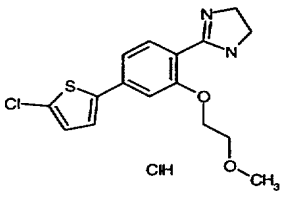
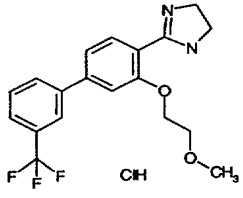
145	
146	
147	
148	
149	
150	
151	
152	

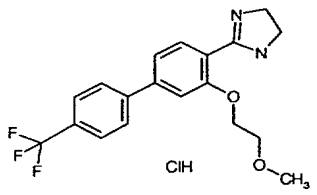
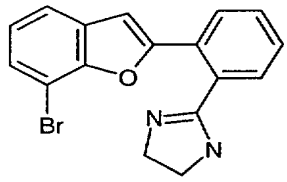
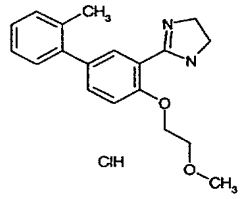
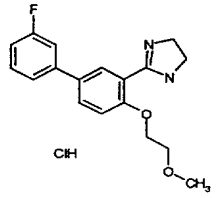
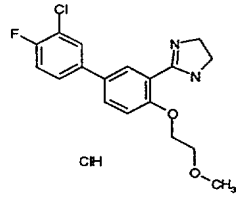
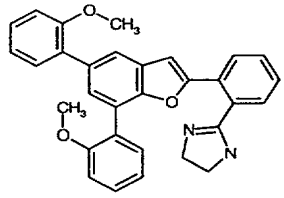
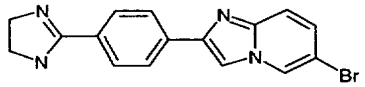
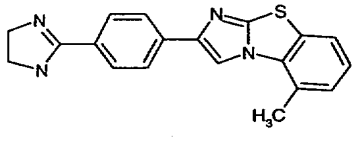
153	
154	
155	
156	
157	
158	
159	
160	

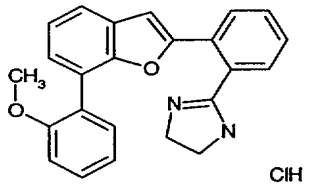
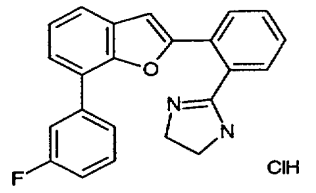
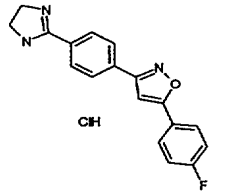
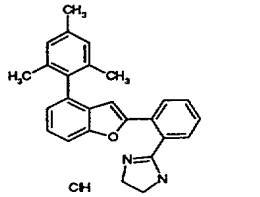
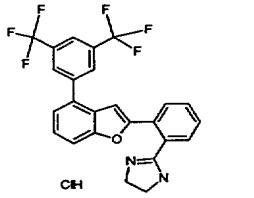
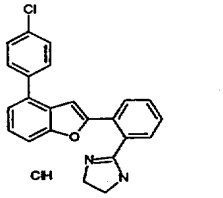
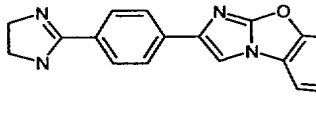
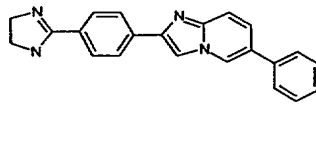
161	
162	
163	
164	
165	
166	
167	
168	

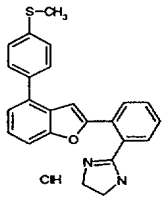
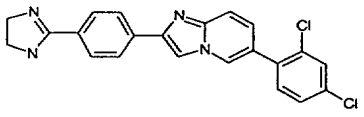
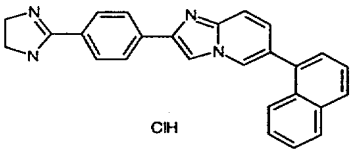
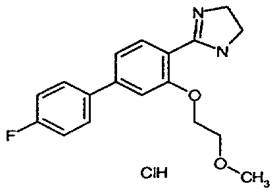
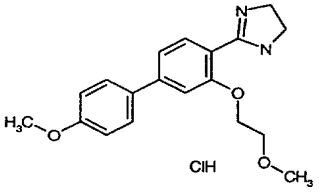
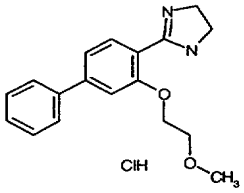
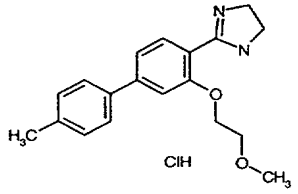
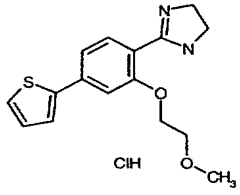
169	
170	
171	
172	
173	
174	
175	
176	

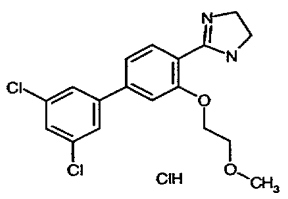
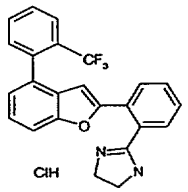
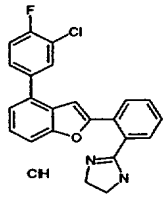
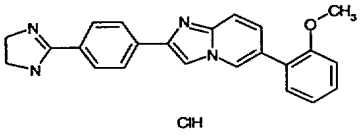
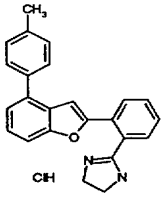
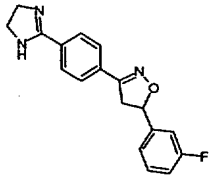
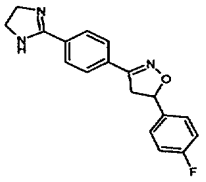
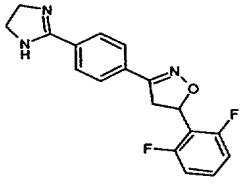
177	
178	
179	
180	
181	
182	
183	
184	

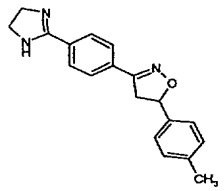
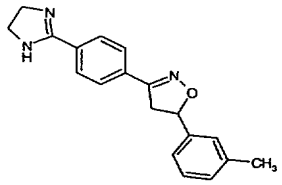
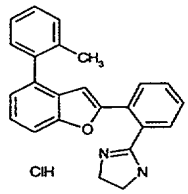
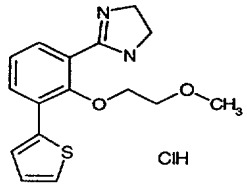
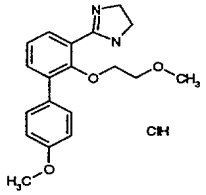
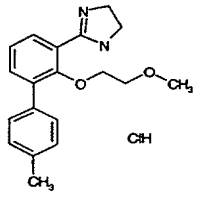
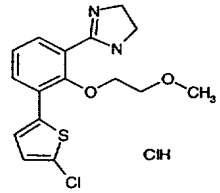
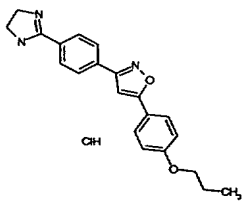
185	
186	
187	
188	
189	
190	
191	
192	

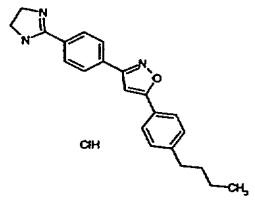
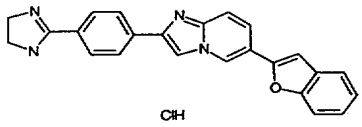
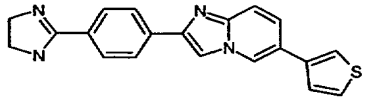
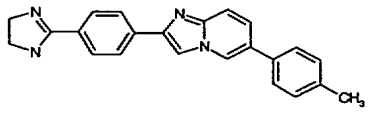
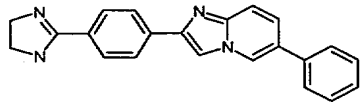
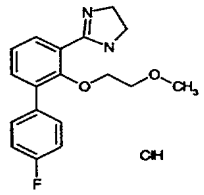
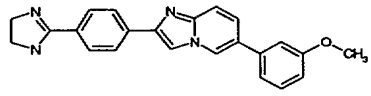
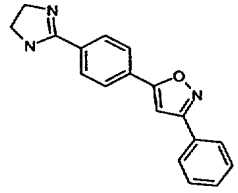
193	
194	
195	
196	
197	
198	
199	
200	

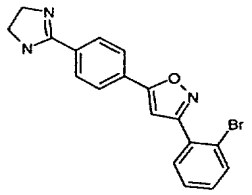
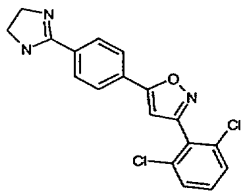
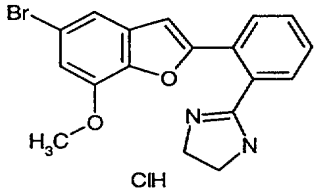
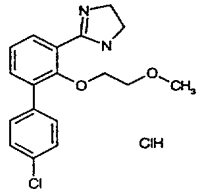
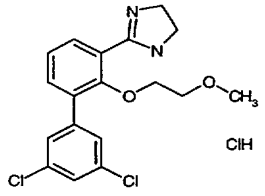
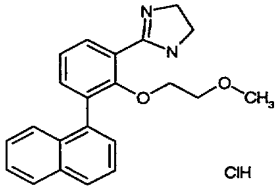
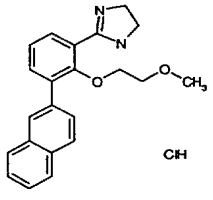
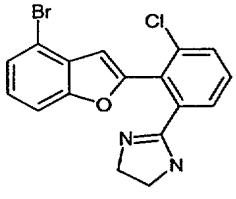
201	
202	
203	
204	
205	
206	
207	
208	

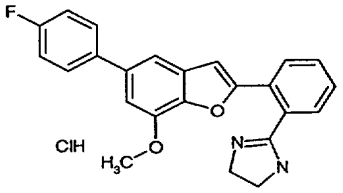
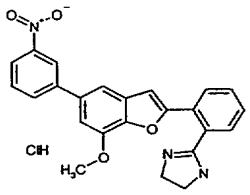
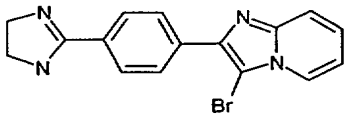
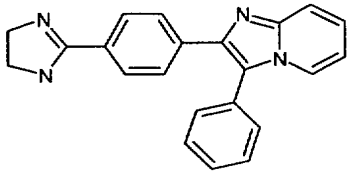
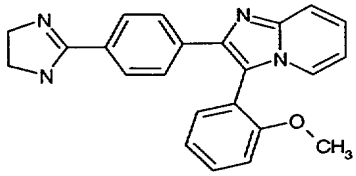
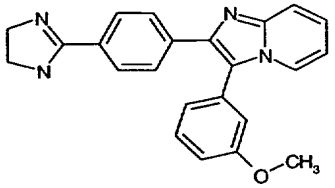
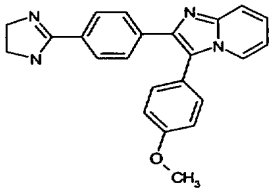
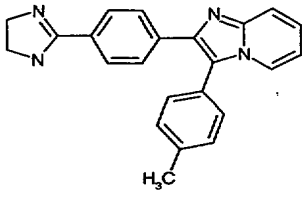
209	
210	
211	
212	
213	
214	
215	
216	

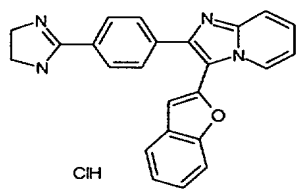
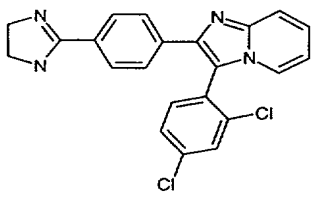
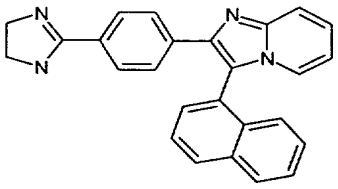
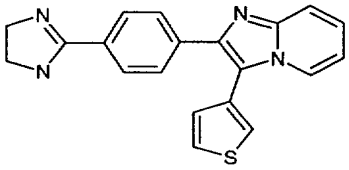
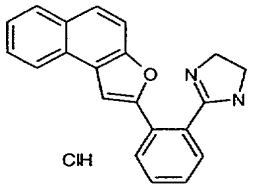
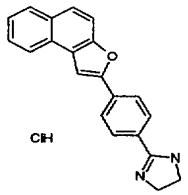
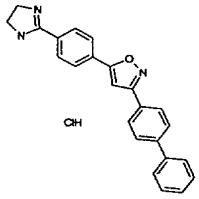
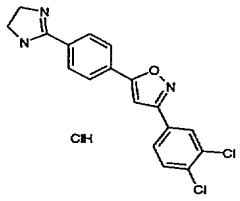
217	
218	
219	
220	
221	
222	
223	
224	

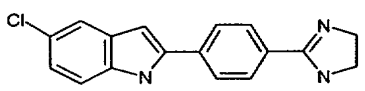
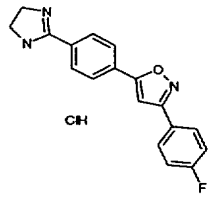
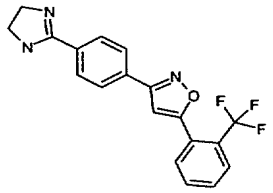
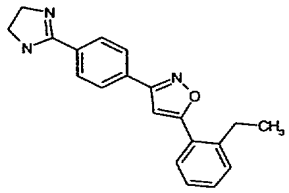
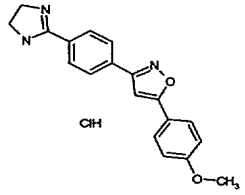
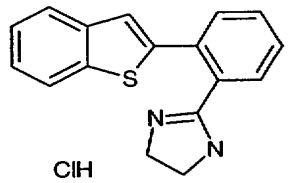
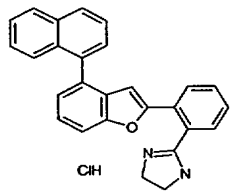
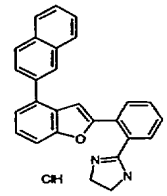
225	
226	
227	
228	
229	
230	
231	
232	

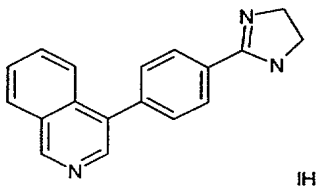
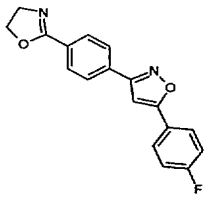
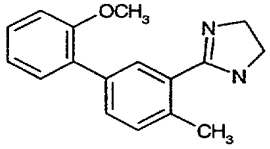
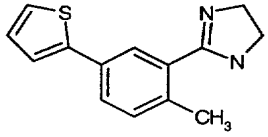
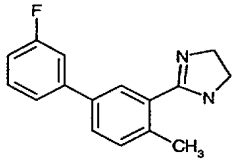
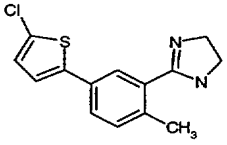
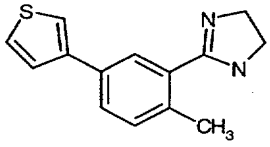
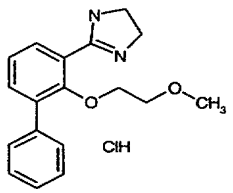
233	
234	
235	
236	
237	
238	
239	
240	

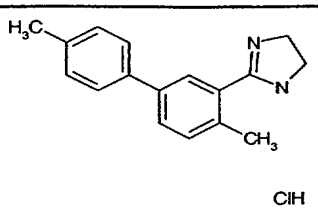
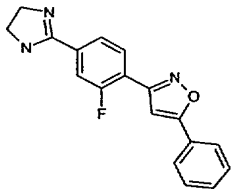
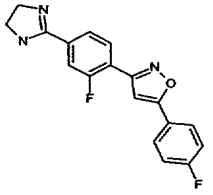
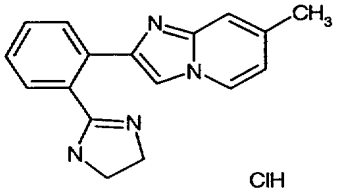
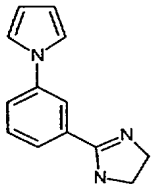
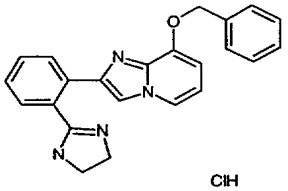
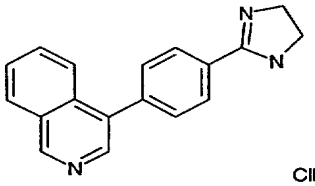
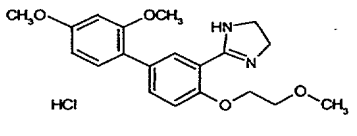
241	
242	
243	
244	
245	
246	
247	
248	

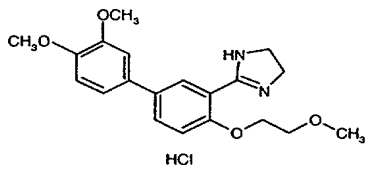
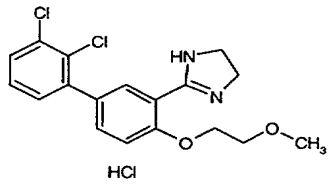
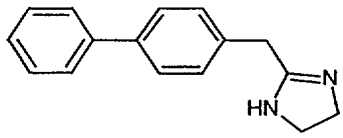
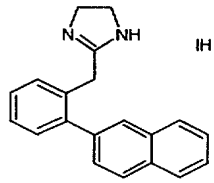
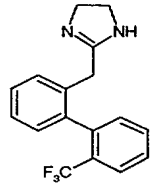
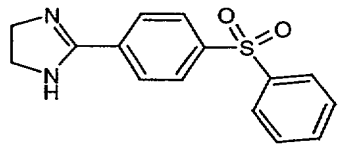
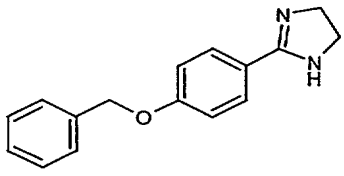
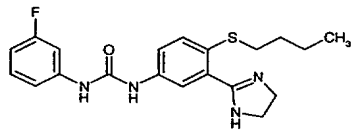
249	
250	
251	
252	
253	
254	
255	
256	

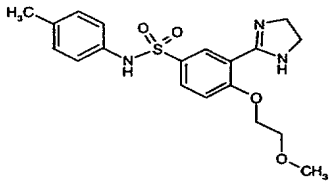
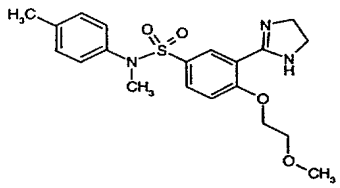
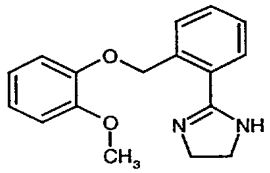
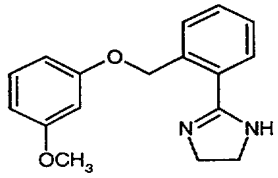
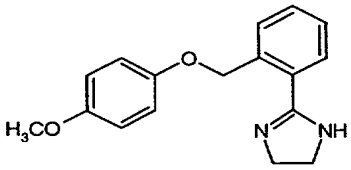
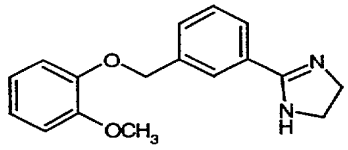
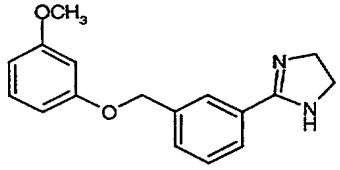
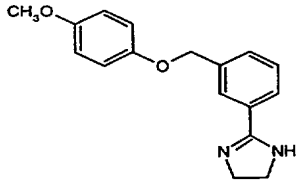
257	
258	
259	
260	
261	
262	
263	
264	

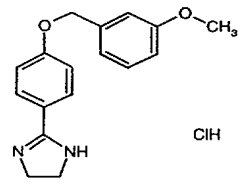
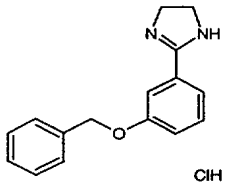
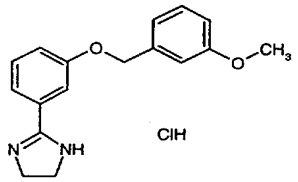
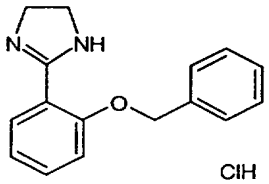
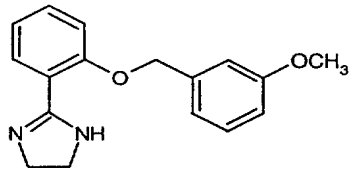
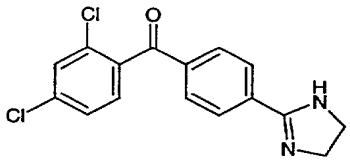
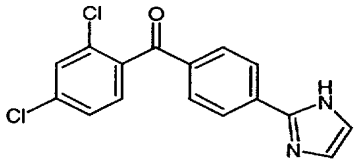
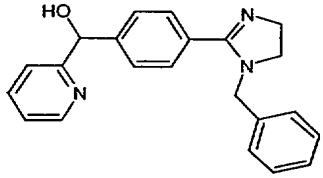
265	
266	
267	
268	
269	
270	
271	
272	

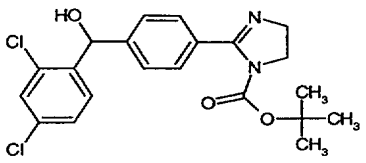
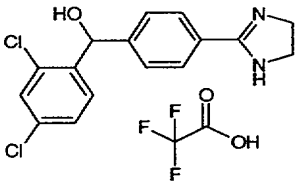
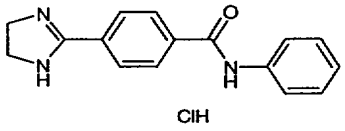
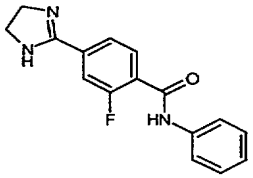
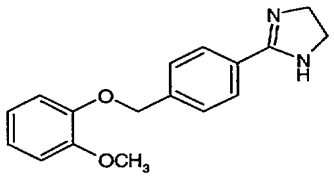
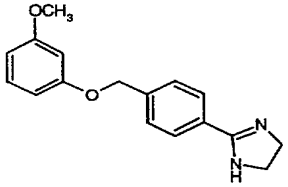
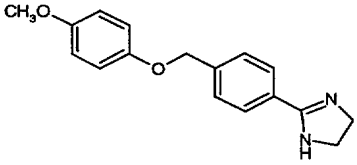
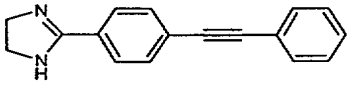
273	 IH
274	
275	 ClH
276	 ClH
277	 ClH
278	 ClH
279	 ClH
280	 ClH

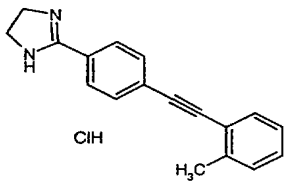
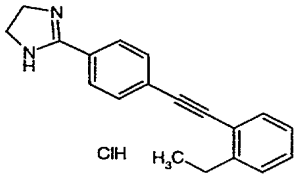
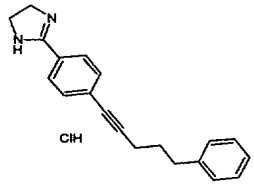
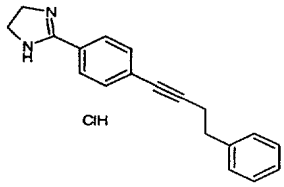
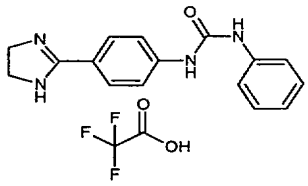
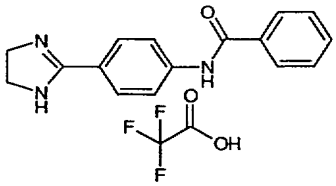
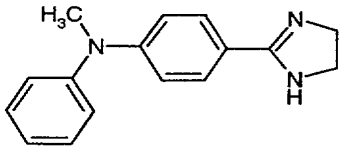
281	 ClH
282	
283	
284	 ClH
285	
286	 ClH
287	 ClH
288	 HCl

289	
290	
291	
292	
293	
294	
295	
296	

297	
298	
299	
300	
301	
302	
303	
304	

305	
306	
307	
308	
309	
310	
311	
312	

313	
314	
315	
316	
317	
318	
319	
320	

321	
322	
323	
324	
325	
326	
327	

By virtue of their acidic moieties, some of the compounds of Formula **I** include the pharmaceutically acceptable base addition salts thereof. Such salts include those derived from inorganic bases such as ammonium and alkali and alkaline earth metal hydroxides, carbonates, bicarbonates, and the like, as well as salts derived from basic organic amines such as aliphatic and aromatic amines, aliphatic diamines, hydroxy alkamines, and the like. Such bases useful in preparing the salts of this invention thus include ammonium hydroxide, potassium carbonate, sodium bicarbonate, calcium hydroxide, methylamine, diethylamine, ethylenediamine, cyclohexylamine, ethanolamine and the like.

Because of a basic moiety, some of the compounds of Formula **I** can also exist as pharmaceutically acceptable acid addition salts. Acids commonly employed to form such salts include inorganic acids such as hydrochloric, hydrobromic, hydroiodic, sulfuric and phosphoric acid, as well as organic acids such as para-toluenesulfonic, methanesulfonic, oxalic, para- bromophenylsulfonic, carbonic, succinic, citric, benzoic, acetic acid, and related inorganic and organic acids. Such pharmaceutically acceptable salts thus include sulfate, pyrosulfate, bisulfate, sulfite, bisulfite, phosphate, mono-hydrogenphosphate, dihydrogenphosphate, metaphosphate, pyrophosphate, chloride, bromide, iodide, acetate, propionate, decanoate, caprylate, acrylate, formate, isobutyrate, heptanoate, propiolate, oxalate, malonate, succinate, suberate, sebacate, fumarate, maleate, 2-butyne-1,4 dioate, 3-hexyne-2, 5-dioate, benzoate, chlorobenzoate, hydroxybenzoate, methoxybenzoate, phthalate, xylenesulfonate, phenylacetate, phenylpropionate, phenylbutyrate, citrate, lactate, hippurate, β-hydroxybutyrate, glycollate, maleate, tartrate, methanesulfonate, propanesulfonate, naphthalene-l-sulfonate, naphthalene-2-sulfonate, mandelate and the like salts.

In addition, it is recognised that compounds of the present invention may form a variety of solvates with a number of different solvents. Representative solvates can be useful as final embodiments of the present invention or as intermediates in the isolation or preparation of the final embodiments of this invention. For example solvates can be prepared with lower alcohols such as ethanol and with alkyl esters such ethylacetate.

It is recognised that various stereoisomeric forms of the compounds of Formula **I** may exist. The compounds may be prepared as racemates and can be conveniently used as such. Therefore, the racemates, individual enantiomers (including, but in no way limited to atropisomers), diastereomers, or mixtures thereof form part of the present invention. Unless otherwise specified, whenever a compound is described or referenced in this specification all the racemates, individual enantiomers, diastereomers, or mixtures thereof are included in said reference or description.

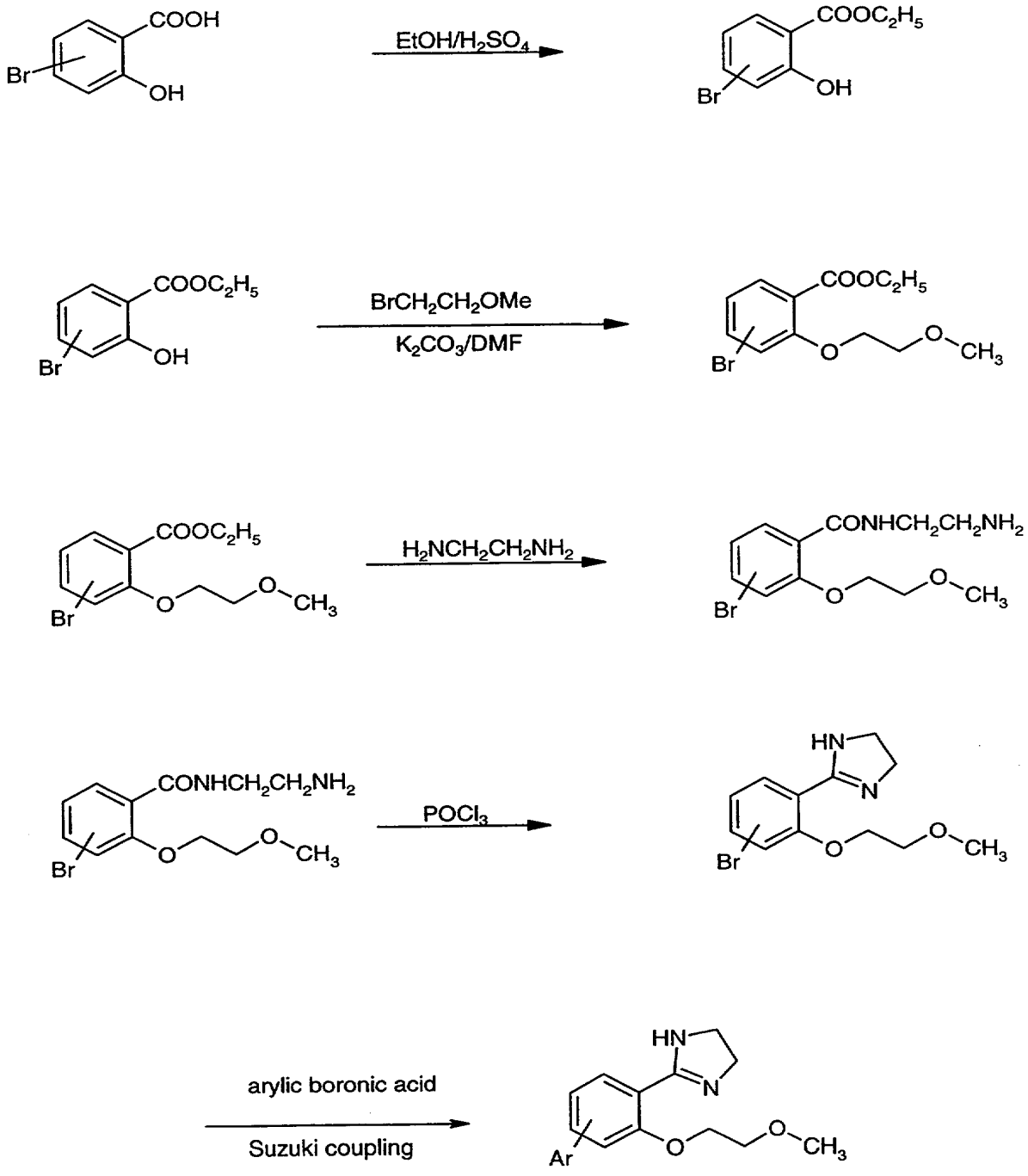
In addition to the pharmaceutically acceptable salts, other salts are included in the invention. They may serve as intermediates in the purification of compounds or in the preparation of other, for example pharmaceutically acceptable, acid addition salts, or are useful for identification, characterisation or purification.

General methods of synthesis for the compounds of the present invention are described in Schemes below.

A general scheme for the synthesis of 3-, 4-, and 5-arylic substituted 2-(2-methoxyethoxy)-
phenyl-4,5-dihydro-1H-imidazoles is generally illustrated by Scheme **I.**

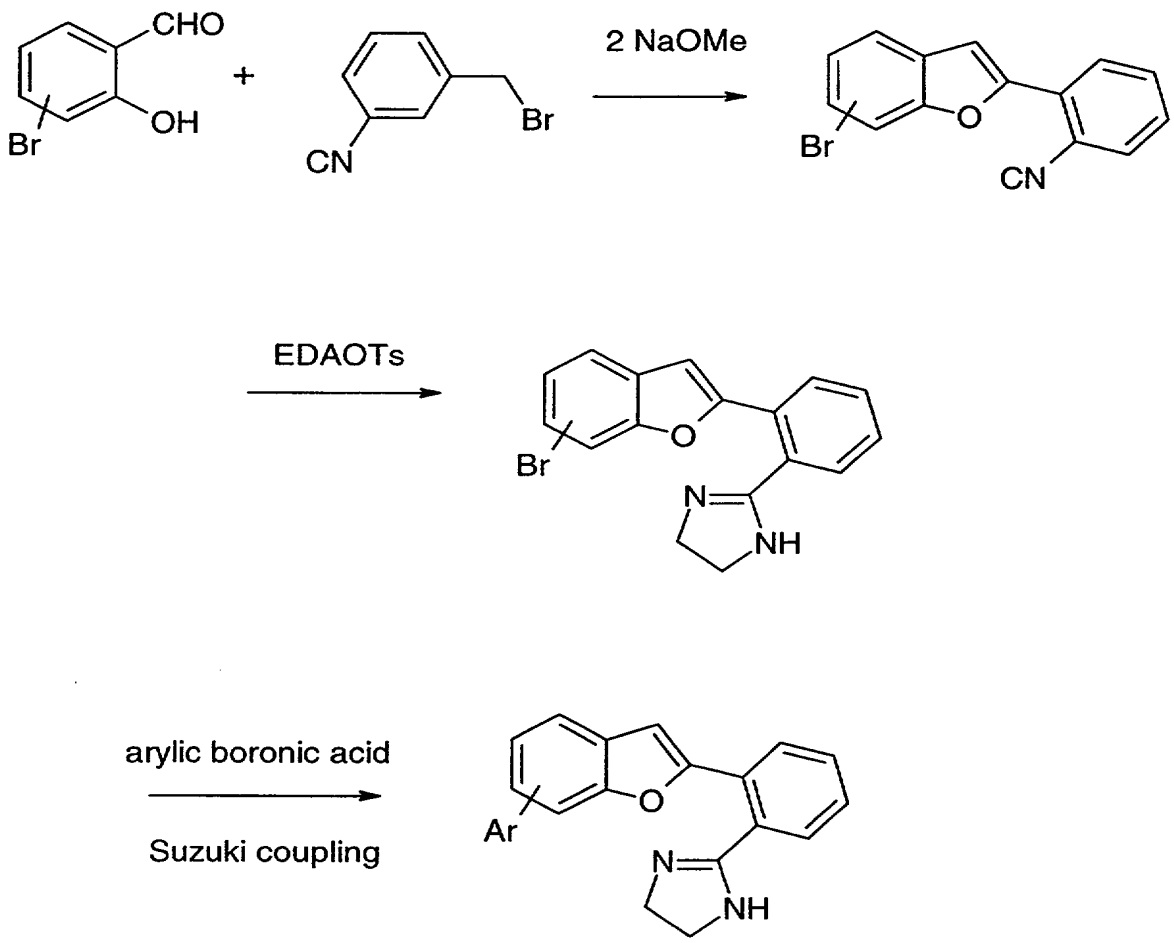
The artisan will appreciate that the methods indicated in Scheme I are standard procedures which are well known in the art. The artisan can select appropriate intermediates and process conditions using the description set forth in Scheme I. The artisan will recognize that the process set forth in Scheme I is more generally applicable to allow preparation of compounds of this invention, provided that the corresponding starting materials are utilized.

Scheme I


COOH
Br
OH
EtOH/H2SO4
COOC2H5
Br
OH
COOC2H5
Br
OH
BrCH2CH2OMe
K2CO3/DMF
COOC2H5
Br
O
O
CH3
COOC2H5
Br
O
O
CH3
H2NCH2CH2NH2
CONHCH2CH2NH2
Br
O
O
CH3
CONHCH2CH2NH2
Br
O
O
CH3
POCl3
HN
N
Br
O
O
CH3
arylic boronic acid
Suzuki coupling
HN
N
Ar
O
O
CH3

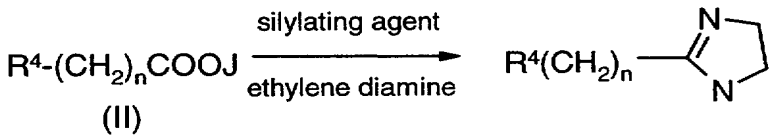
General scheme for the synthesis of 4-, 5- or 7-arylic substituted 2-(2-phenyl-4,5-dihydro-1H-imidazole) benzofuranes

Scheme II



Compounds of Formula **I** wherein X is NH; wherein X is as defined above and the other Formula **I** substituents have the definitions setforth above, can be prepared according to scheme III.

Scheme III



(II)

wherein R^4 and n are as defined herein for Formula **I**, and J is C_{1-8}alkyl, aryl, or aryl C_{1-8}alkyl.

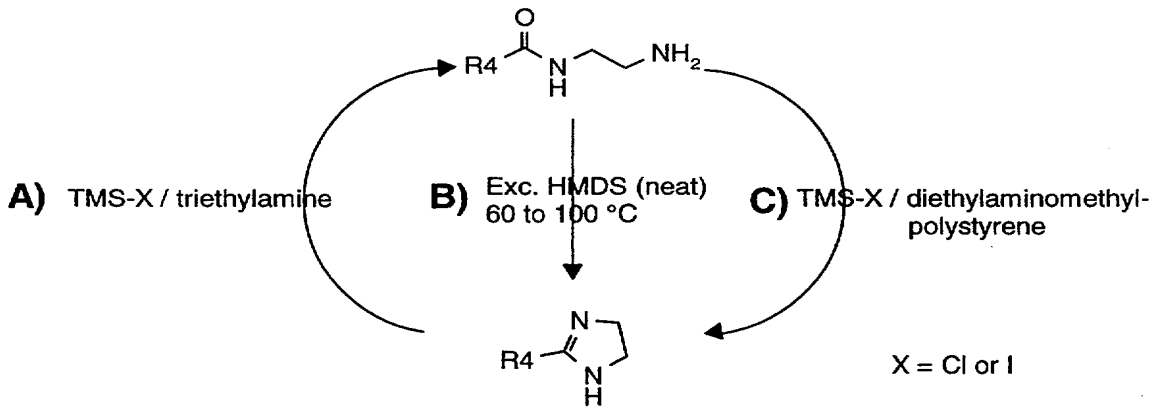
The transformation is further described by Scheme IIIa.

Cyclisation is induced by a silylating agent or a mixture of silylating agents, optionally in the presence of an soluble or insoluble base, e.g. triethyl amine or dimethylaminomethyl polystyrene and a solvent. Useful reagents are e.g. described in FLUKA Chemika, "Silylating Agents" (1995) ISBN 3-905617-08-0 and the literature cited therein.

In a more prefered embodiment, these silylating agents are trimethyl silyl halogenides, TMS-X (e.g. trimethyl silyl chloride or trimethyl silyl iodide) or hexamethyl disilazane, HMDS or trimethyl silyl diethylamine, TMS-DEA or mixtures of them. In the most prefered embodiment the reactions are carried out either in methylene chloride with excess TMS-Cl or, more prefered, TMS-I in presence of triethyl amine or dimethylaminomethyl polystyrene at ambient temperature, or in neat HMDS or HMDS/TMS-Cl 100/1, without additional base and solvent at 50°C to reflux, preferably at 70°C to 90°C. In some cases, using TMS-X as cyclizing reagent, excessive reagent has to be added in several portions within a period of time (up to about a week) to ensure complete conversion. The process described herein is compatible to many functionalities present in an organic molecule, e.g. unprotected hydroxy, unprotected amino, olefinic double bond, cyano, nitro, aromatic halogen,

amide and is successful in some cases, when conventional methods failed (Chem. Pharm. Bull. **1980,** *28*, 1394-1402).

Scheme IIIa



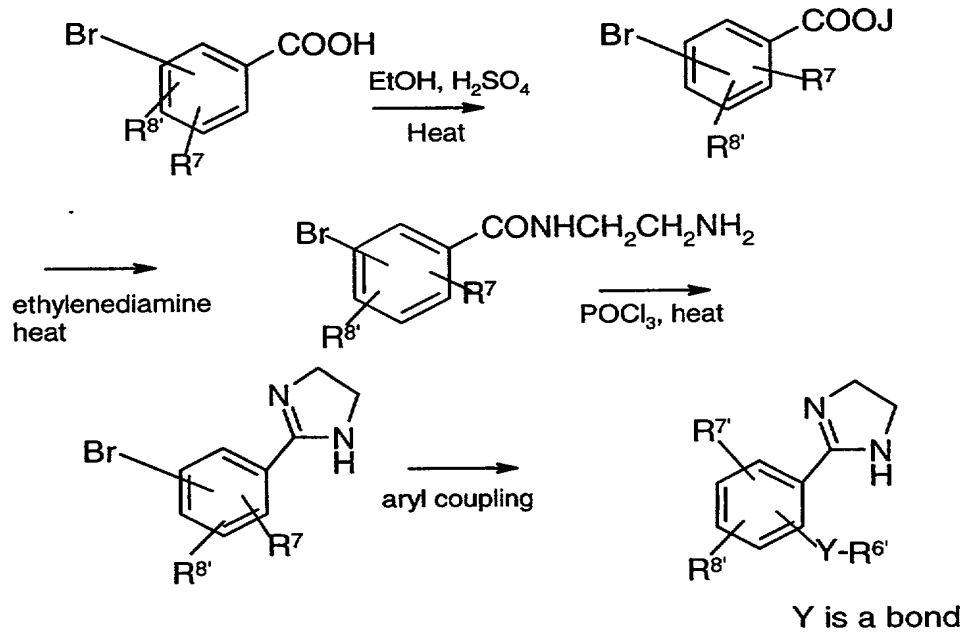
The process described in Scheme IIIa affords numerous advantages over similar methods known in the art. The transformation can be achieved in high yield and under mild conditions, whereas, methods known in the art require the use of extreme conditions or reagents

The artisan will recognise that there are other processes which could be used to prepare desired compounds. See for example, J.Med.Chem. **1990, 33**, 2501-8 (uses $(CH_2NH_2)_2$); J.Chem.Soc. **1947**, 497(uses $(CH_2NH_2)_2$ and TsOH/200-220^{0}C); J.Am.Chem.Soc. **1953**, **75**, 2986-8497(uses $(CH_2NH_2)_2$ and 200-220^{0}C); J.Med.Chem. **1987, 30**, 1482-9 (uses $Al(CH_3)_3$ and $(CH_2NH_2)_2$); Tetrahedron Lett.

1990, **31**, 1771-74(uses $(CH_2NH_2)_2$); J.Org.Chem.**1987**, **52**, 1017-21 ($La(OSO_2CF_3)_3$ and $(CH_2NH_2)_2$); Zh.Prikl.Khim. **1970**, **43**, 1641 (**CA**:73:77138r) (uses $(CH_2NH_2)_2$ and strongly acidic cation exchanger); Arch.Pharm. **1986**, **319**, 830-34 (uses $(CH_2NH_2)_2$); J.Heterocycl.Chem. **1990**, **27**, 803-5 (uses $(CH_2NH_2)_2$); Tetrahedron Lett. **1995**, **51**, 6315-36 (uses two step process with 1) H_2S and MI then 2)$(CH_2NH_2)_2$).

The skilled artisan will also appreciate that a hydroxy substituted group can be used to prepare desired compounds claimed by this invention. Such process is illustrated by Scheme IV below.

Scheme IV



wherein $R^{6'}$, $R^{7'}$and $R^{8'}$ are R^6, R^7 and R^8, respectively, protected derivatives thereof, or precursor moieties thereto.

.

The artisan appreciates that, in some instances, desired isomeric forms may be obtained using separation methods which are generally known.

Compounds of Formula (I) have primary action during hyperglycemia in that they improve glucose tolerance without producing marked reduction in basal plasma glucose levels.

Compounds of the invention were active in screens for activity using assays based on the use of BTC6 cells, for example as described by Poitout,V et al. Diabetes 44:306-313 (1995) and D'Ambra ,R et al Endocrinology, 126: 2815-2822 (1990)] and rat Langerhans islets, for example as described by Lacy, P.E and Kostianovsky,M. Diabetes (1967),and as described in more detail in hereinbelow, and in an Intravenous Glucose Tolerance Test as described hereinbelow.

The invention further includes a method of treating diabetes in which an effective amount of a compound of formula (I) or a pharmaceutically acceptable salt or ester thereof is administered to a patient requiring such treatment.

Preparations and Examples

The following examples and preparations are provided merely to further illustrate the invention. The scope of the invention is not in any way limited or to be construed as merely consisting of the following examples. In the following examples and preparations, melting point, nuclear magnetic resonance spectra, mass spectra, high pressure liquid chromatography over silica gel, gas chromatography, N,N-dimethylformamide, palladium on charcoal, tetrahydrofuran, ethyl acetate, thin layer chromatography and elemental analysis are abbreviated M.Pt. or m.p., NMR, MS, HPLC, GC, DMF, Pd/C, THF, EtOAc, TLC and EA respectively. The terms "EA", "TLC", "NMR", and "MS", when being utilised in the preparations, indicate that the data indicated was consistent with the desired structure. Reported melting points are uncorrected and yields are not optimised.

Ethyl-5-bromo-2-hydroxy-benzoate

A solution of 50 g (230 mmol) 5-bromosalicylic acid in 300 ml dried EtOH and 20 ml

conc. H_2SO_4 was heated at reflux for 8 h. The mixture was cooled to room temperature and treated with water and neutralised with $NaHCO_3$. The aqueous phase was extracted with ethylacetate. The extract was dried and concentrated to give 46 g (81%) of a solid product. (m.p. 51 °C)

Ethyl-5-bromo-2-(2-methoxyethoxy)-benzoate

To a solution of 20 g (81,6 mmol) of the above-mentioned compound in 200 ml dimethylformamide was added 11,28 g (81,6 mmol) potassium carbonate and 13,9 g (100 mmol) (2-bromoethyl)methylether. The mixture was heated at 80 °C for 48 hours. After cooling to room temperature the mixture was added to water and extracted with ethylacetate.
The organic phase was dried and concentrated to give 22,8 g (89%) of a syrup.

Aminoethyl-5-bromo-2-(2-methoxyethoxy)-benzoamide

A mixture of 22,6 g (74,5 mmol) of the above-mentioned compound and 44 g (745 mmol) ethylenediamine was heated for 8 h at 100°C. After cooling to room temperature water (500 ml) was added. The induced solid was separated, washed with water and dried to give
19 g (80%) of an amorphous product.

5-Bromo-2-(2-methoxyethoxy)-phenyl-4,5-dihydro-1H-imidazole

To 18,8 g (59,2 mmol) of the above-mentioned compound was added cautiously phosphorousoxy-trichloride. The mixture was heated for 8 hours at 80-90 °C. After evaporation the mixture was added to ice-water and was made basic with 5 N NaOH and extracted with dichloromethane. The extract was washed with water, dried and

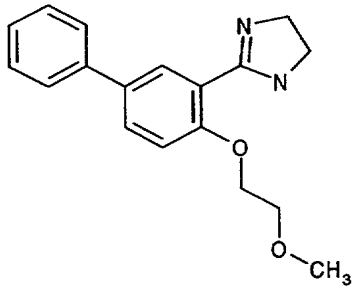
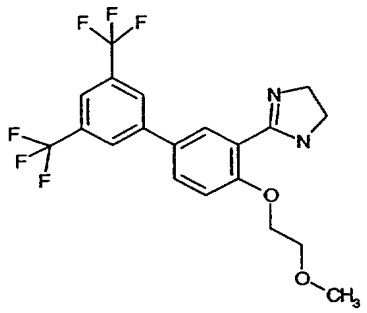
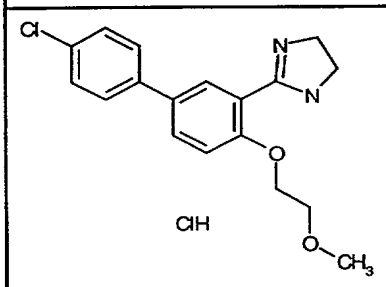
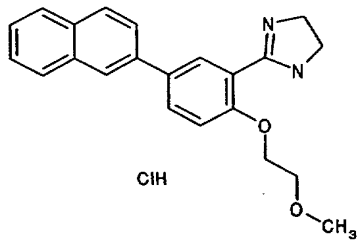
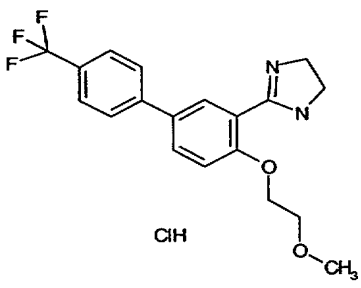
evaporated in vacuo and chromatographed with dichloromethane/ethanole 70/30 on silicagel to give after concentration 10 g (56 %) of a solid product . (mp 182 °C dec.)

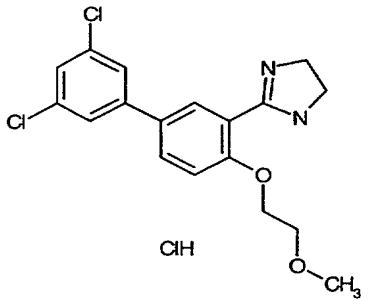
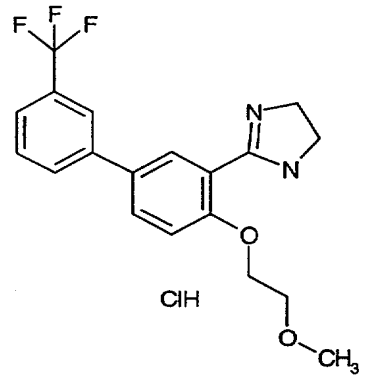
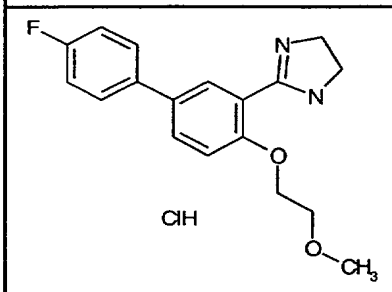
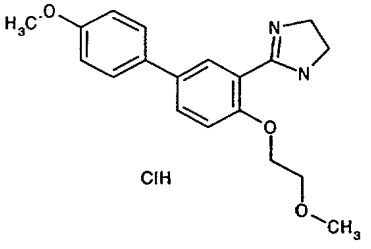
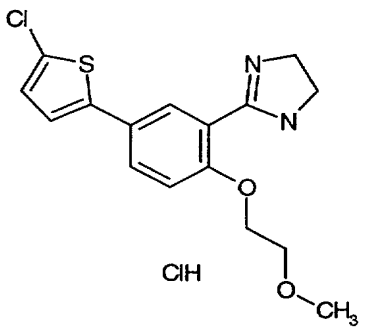
5-(3-Chloro-4-fluoro-phenyl)-2-(2-methoxyethoxy)-phenyl-4,5-dihydro-1H-imidazole

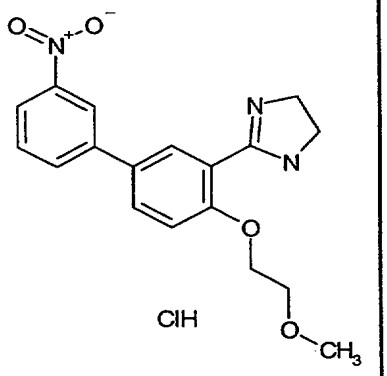
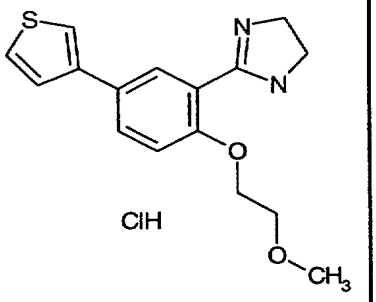
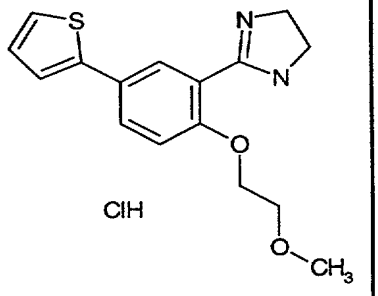
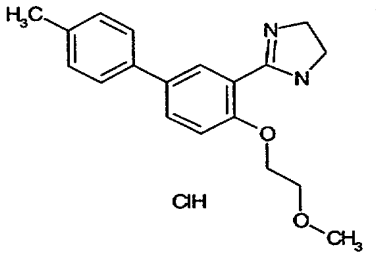
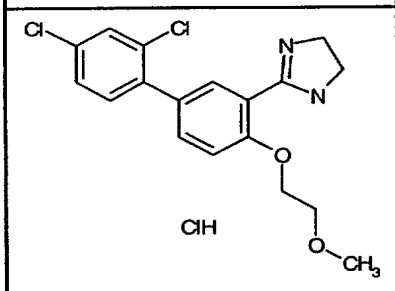
To a solution of 0,4 g (1mmol) of the above-mentioned compound in 20 ml 1,4-dioxan was added under argon 0,115 g (0,1mmol) $Pd(PPh_3)_4$ and 2 ml 2M Na_2CO_3. After addition of 0,244 g (1,5mmol) 5-chloro-2-thiophenboronic acid the mixture was heated to 18 hours at
80 °C. After cooling to room temperature, the solid was filtered off, the solution was acidified with 2N HCl and after evaporation in vacuo chromatographed on silica gel with dichloromethane/ethanol 90/10 giving 0,16 g (36%) of a crystalline product. (mp 204-206 °C)

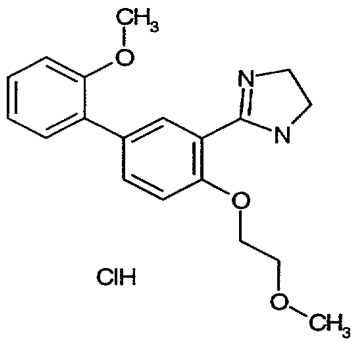
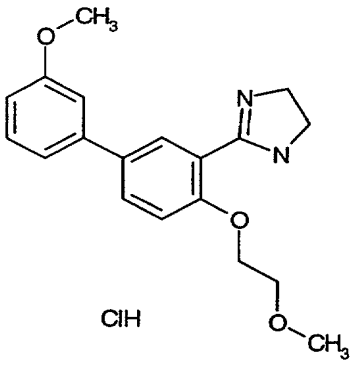
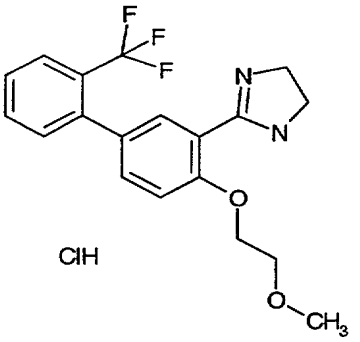
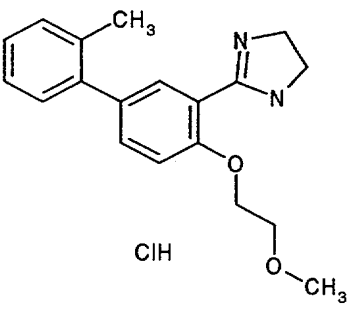
The following examples were prepared in substantial accordance with the above-mentioned examples and the procedures and methods disclose herein.

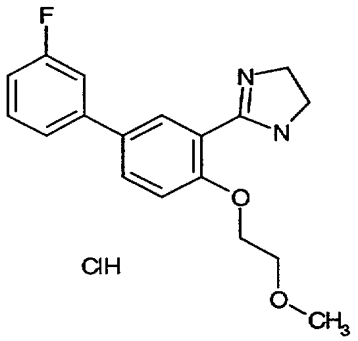
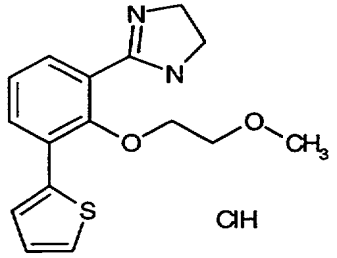
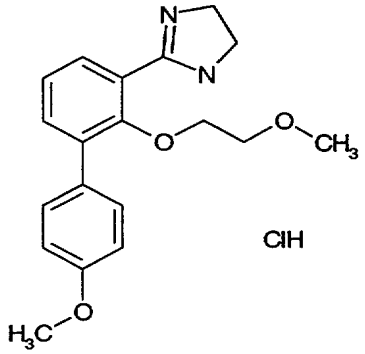
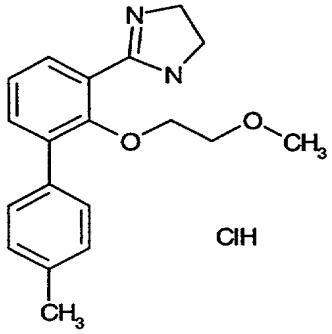
The Examples set forth herein by Table I were prepared using the general synthesis methods illustrated by Scheme I, herein. The corresponding starting materials were used to prepare the compounds set forth below

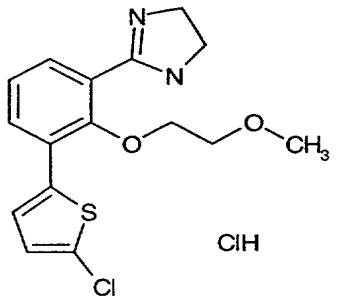
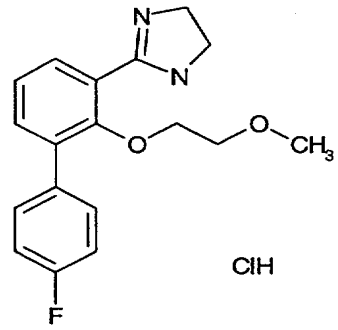
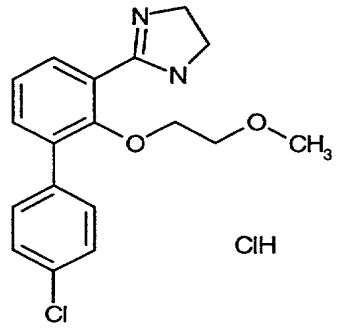
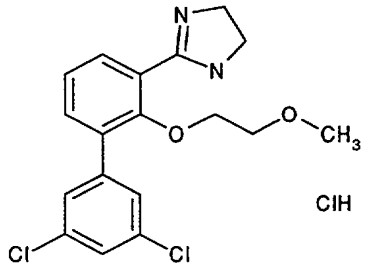
	M^+	mp (°C)	yield(%)
	296	amorphous	24
	432	amorphous	23
	330	amorphous	28
	346	amorphous	18
	364	amorphous	24

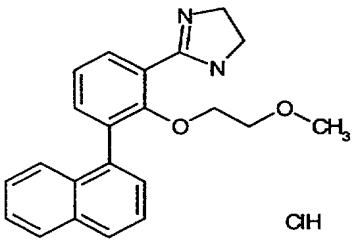
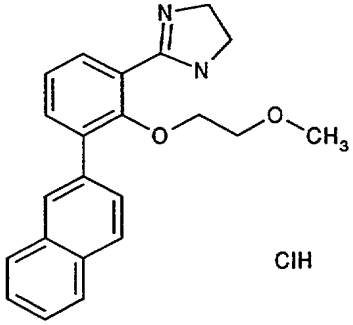
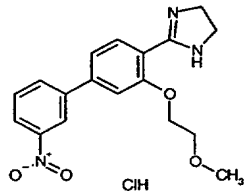
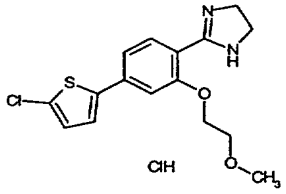
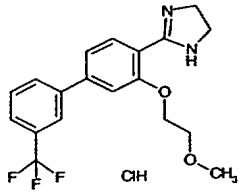
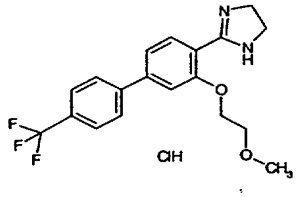
	365	amorphous	18
	364	171-173	21
	314	234-235	38
	326	208-209	33
	336	amorphous	13

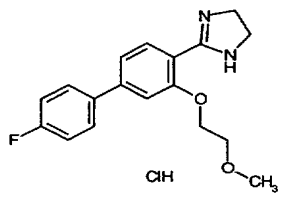
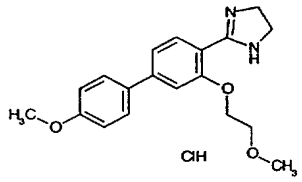
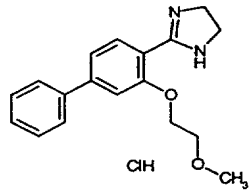
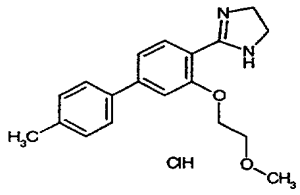
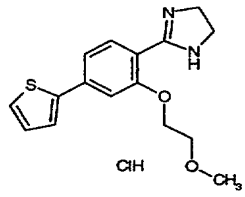
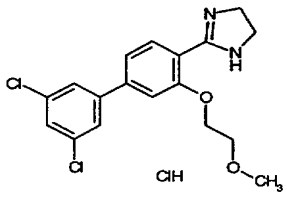
	341	184-186	20
	302	226	30
	302	amorphous	50
	310	amorphous	26
	364	amorphous	37

	326	amorphous	30
	326	amorphous	14
	364	amorphous	22
	310	amorphous	13

	314	amorphous	23
	302	189	10
	326	162-164	9
	310	206-207	15

	336	185-187	22
	314	213-215	24
	330	236-238(dec.)	46
	364	174 (dec.)	25

	346	124-126	22
	346	67-69	22
	341	amorphous	26
	336	amorphous	7
	364	amorphous	37
	364	amorphous	25

	314	190-192	68
	326	202-204	62
	296	202-204	50
	310	198-200	42
	302	210-212	57
	364	210-212	8

A General scheme for the synthesis of **4-, 5- or 7-arylic substituted 2-(2-phenyl-4,5-dihydro-1H-imidazole) benzofuranes** is provided herein above by Scheme II. Examples prepared following the method set forth in Scheme II are set forth herein.

5-Bromo-2-(2-cyanophenyl) benzofurane

To a solution of 6.47 g (3.2 mmol) 5-bromosalicylic aldehyde in dimethylformamide (28 ml) was given at room temperature 1.88 g (3.47 mmol) sodium methoxide in 6 ml ethanol. After stirring at room temperature for 8 hours 1.88 g (3.47 mmol) sodium methoxide in 6 ml ethanol was added and the mixture was heated (70°C) and stirred for 3 hours. After cooling to room temperature the solvents were evaporated , water and dichloromethane was added and the organic phase was dried and concentrated. After additon of ethanol the induced crystalls were filtered and dried. Yield : 2.3 g (25 %), mp 140°C.

5-Bromo-2-(2-(4,5-dihydro-1H-imidazolo) phenyl) benzofurane

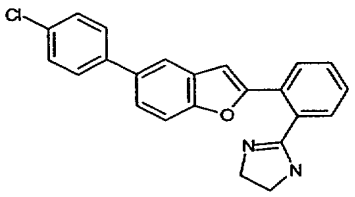
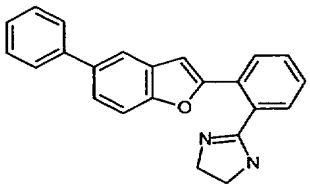
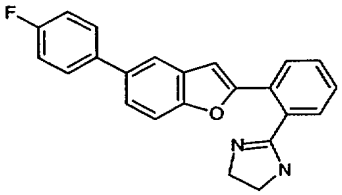
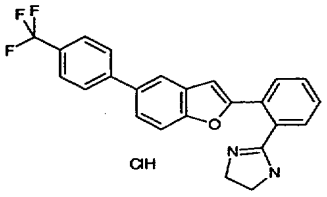
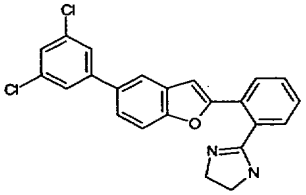
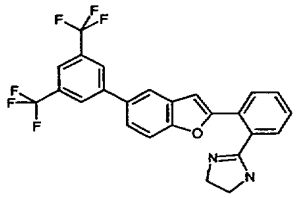
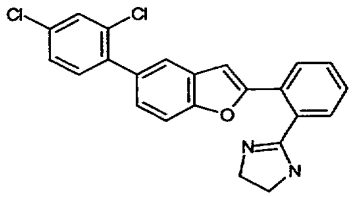
A mixture of 1g (0.33 mmol) of the above-mentioned compound and 0.9 g (0.38 mmol) of ethylenediamine monotosylate was heated at 210°C for 5 hours. After cooling to room temperature water (30 ml) and 2N NaOH (30 ml) was added and the mixture was extracted with dichloromethane. The organic phase was dried with Na_2SO_4 and evaporated giving an oil

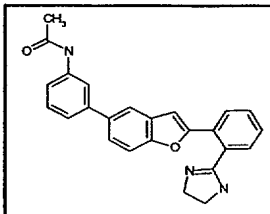
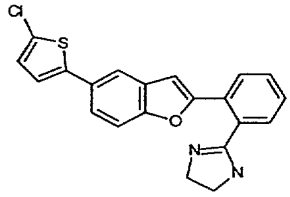
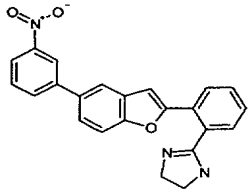
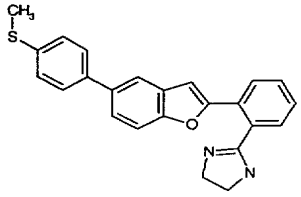
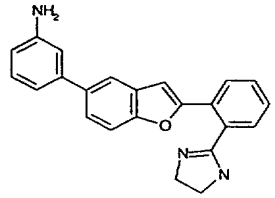
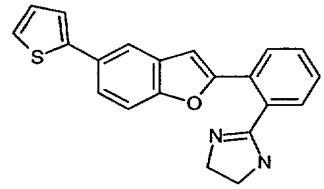
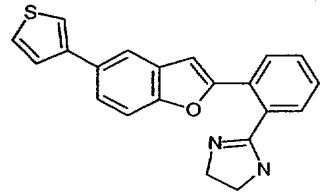
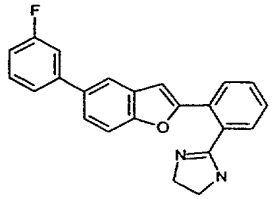
Yield : 0.3 g (26 %).

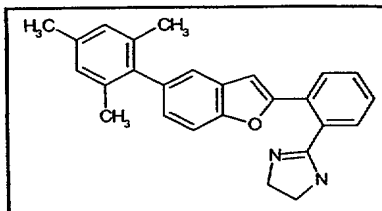
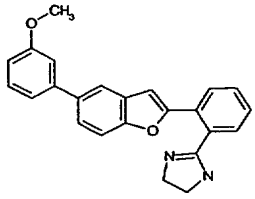
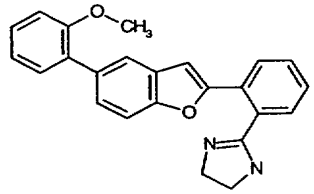
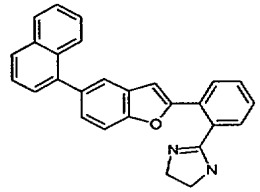
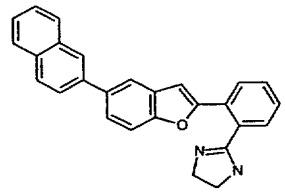
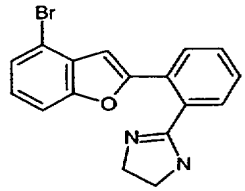
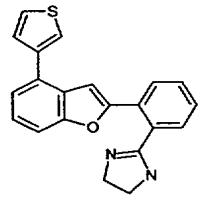
5-(4-Methoxy-phenyl)-2-(2-(4,5-dihydro-1H-imidazolo) phenyl) benzofurane

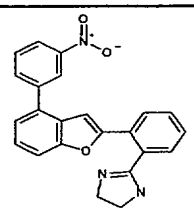
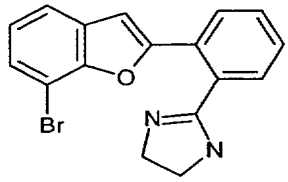
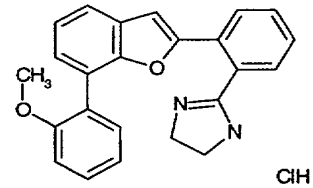
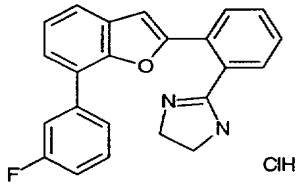
To a solution of 0.322 g (0.94 mmol) of the above-mentioned compound in 1,4-dioxan (15 ml) was added under argon 0.109 g (0.94 mmol) $Pd(PPh_3)_4$ and 2 ml 2 M Na_2CO_3 . After addition of 0.172 g (1.1 mmol) 4-methoxy-phenylboronic acid the mixture was heated 16 hours at 80°C. After cooling to room temperature, the solid was filtered off, the solution was acidified with 2N HCl and after evaporation in vacuo chromatographed on silicagel with isopropanol/ethylacetate/methanol/ammonia in ethanol 40/40/5/10 to give after concentration an amorphous product. Yield : 0.27 g (78%).

The following examples set forth in **Table II** were prepared in substantial accordance with the above-mentioned examples and the procedures and methods disclose herein.

	MS^+	mp	Yield (%)
	372	amorphous	69
	338	oil	70
	356	amorphous	54
	442	> 280 °C	35
	407	273 - 274 °C	81
	474	> 280 °C	59
	407	amorphous	58

	395	amorphous	38
	378	amorphous	71
	383	amorphous	45
	384	180 - 182 °C	34
	353	amorphous	55
	344	amorphous	52
	344	290 °C (Z)	52
	356	298 - 299 °C	46

	380	amorphous	19
	368	amorphous	49
	368	amorphous	40
	388	amorphous	88
	388	amorphous	75
	341	155-156 °C	30
	344	amorphous	79

	383	amorphous	78
	341	amorphous	24
	404	266 - 267 °C	30
	392	215 - 216 °C	19

The pharmacological activity of compounds of the present invention may be determined by methods well known in the art and by the assays disclosed herein.

ASSAYS

BTC6, F7 Insulinoma Cell Screening Models

BTC6,F7 are cultured in DMEM 4.5g/l glucose with the following supplements: 15%(v/v) equine serum; 2.5% (v/v) FCS; and 50 U/ml Penicillin/ 50 µg/ml Streptomycin.

A) Adherent BTC6,F7 cells

BTC6,F7 are seeded after trypsinization to 30.000 cells/well in a 96 well multiplate. The cells grow to 50 % confluence and at day 2 or 3 after seeding, the insulin secretion experiments were performed as follows:

Discard the supernatant of the 96 well plates after the cells have been seeded, wash 3 times with EBSS (Earl's balanced salt solution) (0 mM glucose)/ 0.1 % BSA and incubate in the EBSS solution 30 min at 5% CO_2, 37°C.

The experiments with the compounds were run in the presence of 10 mM glucose and also in the absence of glucose in different concentrations. Incubation time is 1 hour. The supernatante is filtered and the insulin amounts measured by radioimmunoassay using an antibody directed against rat insulin.

B) Dissociated BTC6,F7 cells

BTC6,F7 cells at 50 % confluence were dislodged using enzyme free cell dissociation solution. Dislodged cells were dissociated by pressing the cell suspension through a needle (25 gauge). Cells were washed three times in EBSS (0 mM

glucose)/0.1% BSA and insulin secretion experiments are performed as described above.

Dose response titrations on the agonists described revealed EC_{50} values of < 10 mM, preferably < 1mmol.

Rat Islet Assay

The number of islets of three rats is usually sufficient to test 8 compounds including standards.

Solutions

1. 100 ml EBSS (Earl's balanced salt solution): For example, as commercially available Cat. No. BSS-008-B (Specialty Media) without Glucose & Phenol Red, with 0.1% BSA, other comparable commercially available media are acceptable.

2. 100 ml EBSS/BSA buffer + 130.8 mg D(+)-Glucose monohydrate (MW: 198.17)
(=3.3 mM final concentration).

3. 100 ml EBSS/BSA buffer + 661.8 mg D(+)-Glucose monohydrate (MW: 198.17)
(=16.7 mM final concentration).

4. 100 ml EBSS (Earl's balanced salt solution). For example, as commercially available,Cat. No. BSS-008-B (Specialty Media) without Glucose & Phenol Red, with 0.1% BSA, with 0.6 % DMSO; other comparable solutions may be used as well;

Dilution of compounds:

Each dilution of compound has to be double concentrated as it will be diluted 1 + 1 by EBSS/BSA + Glucose (either high Glucose, 16.7 mM final conc. or low Glucose, 3.3 mM final conc.) in a 24 -well tissue culture plate (or other appropriate tissue culture receptacle, if desired).

A stock solution of the compound to be tested of 10 mM in DMSO is made, and the following solutions made for the compounds to be tested, and for standards.

Tube No.	**Concentration (µM)**	**final Concentration (µM)**	**Dilution (µl)**
1	200	100	40 µl of stock + 2000 µl EBSS/BSA
2	60	30	900 µl of tube 1 + 2100 µl EBSS/BSA
3	20	10	300 µl of tube 1 + 2700 µl EBSS/BSA/ 0.6 % DMSO
4	6	3	300 µl of tube 2 + 2700 µl EBSS/BSA/ 0.6 % DMSO
5	2	1	300 µl of tube 3 + 2700 µl EBSS/BSA/ 0.6 % DMSO
6	0.6	0.3	300 µl of tube 4 + 2700 µl EBSS/BSA/ 0.6 % DMSO
7	0.2	0.1	300 µl of tube 5 + 2700 µl EBSS/BSA/ 0.6 % DMSO
8	0.06	0.03	300 µl of tube 6 + 2700 µl EBSS/BSA/ 0.6 % DMSO

Culture dishes are prepared (untreated, 100 x 20 mm, one per two compounds) with 10 ml EBSS/BSA and 10 ml low glucose EBSS/BSA or similar preparative solution and place in an incubator at 37°C, 5 % CO_2, for at least 15 min.

Preparation of Rat islets in culture dishes:

Approximately half of an islet is selected with a 100 µl pipette and transfered to a prepared culture dishe with EBSS/BSA/low Glucose by using binoculars (magnification about 30 x.

The dish is put back into the incubator (37°C, 5 % CO_2) for preincubation (30 min)

If a 24 well plate is used for the assay, the dilutions are distributed (500 µl each) as shown in the scheme below.

500 µl of EBSS/BSA + 0.6 % DMSO (0 = Control).

0 1	**0** 2	**0.03** 3	**0.03** 4	**0.1** 5	**0.1** 6
0.3 7	**0.3** 8	**1** 9	**1** 10	**3** 11	**3** 12
10 13	**10** 14	**30** 15	**30** 16	**0** 17	**0** 18
0.1 19	**0.1** 20	**1** 21	**1** 22	**10** 23	**10** 24

EBSS/BSA/ high Glucose, 500 µl is added to wells 1-16, and EBSS/BSA/ low Glucose, 500 µl is added to wells 17-24.

This scheme is repeated with the other compounds in tissue culture plates and the plates are placed into the incubator (37°C, 5 % CO_2) for at least 15 min.

The culture dish with the second half of the islets is taken out of the incubator. The rest of the islet is picked up with a 100 µl pipette and placed into the second of the prepared culture dishes with EBSS/BSA/low Glucose using binoculars, and placed back into the incubator (37°C, 5 % CO_2) for preincubation (30 min).

Take out the tissue culture plates 1 and 2 and the first preincubated islets. Place 8 islets into each well by using a 10 µl pipette and binoculars (general guideline-magnification about 40 x), generally trying to select islets of similar size which are not digested. The plates are placed back in the incubator (37°C, 5 % CO_2) for 90 min.

Remove the second of the overnight cultured culture dishes with islets from incubator. Approximately half of the islets are placed into the 3rd of the prepared culture dishes with EBSS/BSA/low Glucose with a 100 µl pipette and using binoculars (general guideline-magnification about 30 x), then placed back into the incubator (37°C, 5 % CO_2) for preincubation (30 min).

The 24 -well tissue culture plates 3 and 4 and the second preincubated islets culture dish are removed from the incubator and 8 islets placed into each well by using a 10 µl pipette and binoculars (magnification about 40 x), again selecting islets of similar size which are not digested. Put the plates back to the incubator (37°C, 5 % CO_2) for 90 min.

Take the culture dish with the second half of the islets out of the incubator. with a 100 µl pipette into the 4th of the prepared culture dishes with EBSS/BSA/low Glucose by using binoculars (magnification about 30 x) and put them back into the incubator (37°C, 5 % CO_2) for preincubation (30 min)

Take out the 24 -well tissue culture plates 5 and 6 and the 3rd preincubated islets culture dish. Place 8 islets into each well with a 10 µl pipette by using binoculars (magnification about 40 x). Put the plates back into the incubator (37°C, 5 % CO_2) for 90 min.

Take out the 24 -well tissue culture plates 7 and 8 and the last preincubated islets culture dish. Place 8 islets into each well with a 10 µl pipette by using binoculars (magnification about 40 x). Put the plates back to the incubator (37°C, 5 % CO_2) for 90 min.

When 90 minutes of incubation are over, transfer approximately 300 µl of each well into one well of the 96 well filter plate and by using a vacuum pump filter it

into a 96 well Microplate. 4 of the 24 -well tissue culture plates cover one filterplate and

96-well-Microplate.

The insulin secreted by the islets is measured in a RIA after dilution (1:5).

Intravenous Glucose Tolerance Test

This test is used to examine in vivo efficacy of compounds of the present invention on insulin secretion and blood glucose at hyperglycemia.

The intravenous glucose tolerance test (IVGTT) is performed in overnight fasted anesthetized male wistar rats weighing 280-350g. Under pentobarbitone anesthesia (50 mg/kg ip) polyethylene catheters are placed in the left jugular vein and in the left common carotid artery. Glucose (10% solution) is administered intravenously at a dose of 0.5 g/kg, followed directly by an iv injection of the compound to be tested.

Blood samples are drawn before and 3, 6, 10, 15, 30 and 45 min after glucose administration, centrifuged and the obtained serum is stored at -20°C for analytics. Test compounds are examined along with a reference (positive control) and a vehicle control with n=8 animals per group. Glucose is determined by the hexokinase method, and insulin via radioimmunoassay (RIA) from serum.

In order to examine the effects of test compounds on insulin and blood glucose at euglycemia in vivo, the protocol of the IVGTT as described above is used except for the administration of intravenous glucose.

The compounds of Formula **I** are preferably formulated prior to administration. Therefore, yet another embodiment of the present invention is a

pharmaceutical formulation comprising a compound of Formula **I** and one or more pharmaceutically acceptable carriers, diluents or excipients.

The present pharmaceutical formulations are prepared by known procedures using well-known and readily available ingredients. In making the compositions of the present invention, the active ingredient will usually be mixed with a carrier, or diluted by a carrier, or enclosed within a carrier which may be in the form of a capsule, sachet, paper or other container. When the carrier serves as a diluent, it may be a solid, semisolid or liquid material which acts as a vehicle, excipient or medium for the active ingredient. Thus, the compositions can be in the form of tablets, pills, powders, lozenges, sachets, cachets, elixirs, suspensions, emulsions, solutions, syrups, aerosol (as a solid or in a liquid medium), soft and hard gelatin capsules, suppositories, sterile injectable solutions and sterile packaged powders.

Some examples of suitable carriers, excipients, and diluents include lactose, dextrose, sucrose, sorbitol, mannitol, starches, gum acacia, calcium phosphate, alginates, tragacanth, gelatin, calcium silicate, microcrystalline cellulose, polyvinylpyrrolidone, cellulose, water syrup, methyl cellulose, methyl and propylhydroxybenzoates, talc, magnesium stearate and mineral oil. The formulations can additionally include lubricating agents, wetting agents, emulsifying and suspending agents, preserving agents, sweetening agents or flavoring agents. The compositions of the invention may be formulated so as to provide quick, sustained or delayed release of the active ingredient after administration to the patient.

The compositions are preferably formulated in a unit dosage form, each dosage containing from about 0.1 to about 500 mg, more usually about .5 to about 200 mg, of the active ingredient. However, it will be understood that the therapeutic dosage administered will be determined by the physician in the light of the relevant circumstances including the condition to be treated, the choice of compound to be administered and the chosen route of administration, and therefore the above dosage ranges are not intended to limit the scope of the invention in any way. The compounds can be administered by a variety of routes including the oral, rectal, transdermal, subcutaneous, topical, intravenous, intramuscular or intranasal routes. For all indications, a typical daily dose will contain from about 0.05 mg/kg to about

20 mg/kg of the active compound of this invention. Preferred daily doses will be about 0.1 to about 10 mg/kg, ideally about 0.1 to about 5 mg/kg. However, for topical administration a typical dosage is about 1 to about 500 mg compound per cm^2 of an affected tissue. Preferably, the applied amount of compound will range from about 30 to about 300 mg/cm^2, more preferably, from about 50 to about 200 mg/cm^2, and, most preferably, from about 60 to about 100 mg/cm^2.

The following formulation examples are illustrative only and are not intended to limit the scope of the invention in any way.

Formulation 1

Hard gelatin capsules are prepared using the following ingredients:

	Quantity (mg/capsule)
Active ingredient	25
starch, dried	425
magnesium stearate	10
Total	460 mg

The above ingredients are mixed and filled into hard gelatin capsules in 460 mg quantities.

Formulation 2

Tablets each containing 10 mg of active ingredient are made up as follows:

Active ingredient	10 mg
Starch	160 mg
Microcrystalline cellulose	100 mg
Polyvinylpyrrolidone (as 10% solution in water)	13 mg
Sodium carboxymethyl starch	14 mg

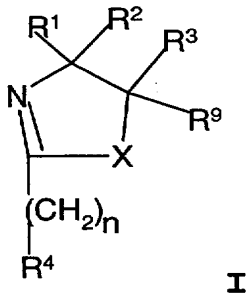
Magnesium stearate	3 mg
Total	300 mg

The active ingredient, starch and cellulose are mixed thoroughly. The solution of polyvinylpyrrolidone is mixed with the resultant powders and passed through a sieve. The granules so produced are dried and re-passed through a sieve. The sodium carboxymethyl starch and magnesium stearate are then added to the granules which, after mixing, are compressed on a tablet machine to yield tablets each weighing 300 mg.

The principles, preferred embodiments and modes of operation of the present invention have been described in the foregoing specification. The invention which is intended to be protected herein, however, is not to be construed as limited to the particular forms disclosed, since they are to be regarded as illustrative rather than restrictive. Variations and changes may be made by those skilled in the art without departing from the spirit of the invention.

We claim

1. A compound of Formula (I):



I

wherein

R^1, R^2, R^3, and R^9 are each independently hydrogen or C_{1-8} alkyl; or

R^1 and R^3, together with the carbon atoms to which they are attached, combine to form a C_{3-7} carbocyclic ring and R^2 and R^9 are each independently hydrogen or C_{1-8} alkyl; or

R^1 and R^3, together optionally form a bond and R^2 and R^9 are each independently hydrogen or C_{1-8} alkyl; or

R^1 and R^2, together with the carbon atom to which they are attached combine to form a C_{3-7} spirocarbocyclic ring and R^3 and R^9 are each independently hydrogen or C_{1-8} alkyl; or

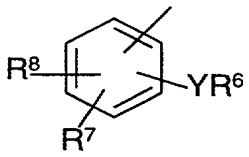
R^3 and R^9, together with the carbon atom to which they are attached, combine to form a C_{3-7} spirocarbocyclic ring and R^1 and R^2 are each independently hydrogen or C_{1-8} alkyl;

X is -O-, -S-, or $-NR^5-$;

R^5 is selected from the group consisting of hydrogen, C_{1-8} alkyl, optionally substituted aryl, and an amino protecting group;

n is 0, 1, or 2;

R^4 is a group of the formula:



Y is selected from the group consisting of a bond, $-O(CH_2)_k-$, $-(CH_2)_kO-$, -CO-, -CHOH-, -CONR-, -NRCO-, -NR'CONR''-, $-(CH_2)_kW(CH_2)_{R''''}-$, $-C\equiv C(CH_2)_k-$, $-(CH_2)_kC\equiv C-$, $-CH=CH(CH_2)_k-$, $-(CH_2)_kC=CH-$, NR'''', SO_2, SO_2NR'', and $NR'''SO_2$; wherein $-(CH_2)_kW(CH_2)_b-$ is optionally substituted with C alkyl or hydroxy;

k is independently 0, 1, 2, 3, or 4;

b is independently 0, 1, 2, 3, or 4;

provided that the sum of k and b together is not more than 4;

W is selected from the group consisting of a bond, O, S, SO_2, SO, SO_2NR'', NR'' SO_2, NR'', CONR', NR'CO, -C=C-, -C≡C-, C=O, and NR''''CONR'''';

R, R', R'' and R''' are each independently selected from the group consisting of hydrogen, C_{1-4} alkyl, and benzyl;

R'''' is selected from the group consisting of of hydrogen, C_{1-8} alkyl, benzyl, and an amino protecting group;

R^8 is selected from the group consisting of hydrogen,

C_{1-8} alkyl, C_{1-8} alkoxy, C_{3-7} cycloalkyl, C_{3-7} cyclo C_{1-8} alkoxy, hydroxy, halo, carbo C_{1-8} alkoxy, halo C_{1-6} alkyl, halo-C_{1-8} alkoxy, optionally substituted phenyl C_{1-8} alkyl;

R^7 is selected from the group consisting of hydrogen, C_{1-8} alkyl, C_{1-8} alkoxy, C_{3-7} cycloalkyl, C_{3-7} cyclo C_{1-8} alkoxy, hydroxy, halo, carbo C_{1-8} alkoxy, halo C_{1-6} alkyl, halo-C_{1-8} alkoxy, optionally substituted phenyl C_{1-8} alkyl, optionally substituted phenyloxy, optionally substituted phenyl C_{1-8} alkoxy, optionally substituted naphthyl, optionally substituted heteroaryl, (tetrahydropyran-2-yl)methoxy, C_{1-8} alkyl-$S(O)_m$, optionally substituted aryl-C_{1-8} alkyl-$S(O)_{m'}$, $CH_3(CH_2)_p$-Z^1-$(CH_2)_q$-Z^2-, and Z^3-$(CH_2)q'$-Z^2-;

where

Z^1 and Z^2 are each independently a bond, -O-, -S-,  , SO_2, sulphoximino, or NR^{13};

Z^3 is hydroxy, protected hydroxy, $NR^{14}R^{15}$, protected amino, SH, or protected SH;

R^6 is selected from the group consisting of optionally substituted phenyl, optionally substituted naphthyl, optionally substituted heteroaryl, and optionally substituted 4,5-dihydroisoxazolinyl;

R^{13}, R^{14} and R^{15} are each independently selected from the group consisting of hydrogen, C_{1-8} alkyl, optionally substituted aryl C_{1-8} alkyl, and optionally substituted phenyl; or R^{14} and R^{15} together with the nitrogen atom to which they are attached may combine to form a heterocyclic ring comprising the nitrogen and C_{2-6} alkyl, wherein C_{2-6}alkyl is optionally substituted with one or two C_{1-8} alkyl groups

or one carbon atom of the heterocyclic ring is optionally replaced by oxygen or sulfur;

p is 0, 1, 2, 3, or 4;

q and q' are each independently selected from the group consisting of 1, 2, 3, 4, and 5;

m and m' are each independently selected from the group consisting of 0, 1 and 2; and

provided that when X is NH and Y is a bond, then R is not unsubstituted phenyl or , 1-phenyl-1-cyclohexylmethyl or phenyl substituted by halo, C_{1-6} alkylthio, C_{1-6} alkyl, $-CF_3$, phenyl, acylamino, aminosulfonyl, methoxy, indol-5-yl, 1-phenyl-1-cyclohexylmethyl, phenyl, or C_{1-6} alkyl subsituted aminosulfonyl;

pharmaceutically acceptable salts and esters thereof.

2. A compound of claim 1 wherein R^1 and R^2 are each hydrogen and R^3 and R^9 are each hydrogen or methyl.
3. R^6 is aryl-C_{1-8} alkyl, unsubstituted naphthyl, optionally substituted heteroaryl.
4. A pharmaceutical formulation comprising a compound according to any one of the preceding Claims or a pharmaceutically acceptable salt or ester thereof, together with a pharmaceutically acceptable carrier or diluent therefor.
5. A compound according to Claim 1 or a pharmaceutically acceptable salt or ester thereof, for use as a pharmaceutical.
6. A compound according to Claim 1 or a pharmaceutically acceptable salt or ester thereof, for use in the manufacture of a medicament for the treatment of a mammal for diabetes, diabetic complications, metabolic disorders, or related diseases where impaired glucose disposal is present.

The Patent Office

INVESTOR IN PEOPLE

Application No: GB 9914222.6
Claims searched: 1 at least

Examiner: Peter Davey
Date of search: 18 October 1999

Patents Act 1977
Search Report under Section 17

Databases searched:

UK Patent Office collections, including GB, EP, WO & US patent specifications, in:

UK Cl (Ed.Q): C2C

Int Cl (Ed.6): C07D

Other: Online: CAS ONLINE

Documents considered to be relevant:

Category	Identity of document and relevant passage		Relevant to claims
X	GB 2095663 A	(WELLCOME), see eg. Ex. 1a	1 at least
X	WO 96/15126 A1	(GEORGIA STATE UNIV.), see eg. Exs. 3, 4, 8, 9, 12 and 14	"
X	WO 96/04241 A1	(FUJISAWA), see eg. Preparation 10	"
X	WO 95/00468 A1	(OTSUKA), see eg. Table 1	"
X	US 5557002	(EISAI), see eg. Exs. 1-11	"
X	US 5210206	(ABBOTT LABS.), see eg. Exs. 3-5	"
X	Chemical Abstracts 127:185367		"
X	Chemical Abstracts 96:135352		"

X	Document indicating lack of novelty or inventive step	A	Document indicating technological background and/or state of the art.
Y	Document indicating lack of inventive step if combined with one or more other documents of same category.	P	Document published on or after the declared priority date but before the filing date of this invention.
&	Member of the same patent family	E	Patent document published on or after, but with priority date earlier than, the filing date of this application.

DERWENT-ACC-NO: 2001-052463

DERWENT-WEEK: 200122

TITLE: New dihydroimidazole, dihydro-oxazole and dihydrothiazole derivatives are useful for treatment of diabetes, diabetic complications, metabolic disorders and diseases where impaired glucose disposal is present

INVENTOR: PAAL M; RUEHTER G ; SCHOTTEN T ; STENZEL W

PATENT-ASSIGNEE: LILLY & CO ELI[ELIL] , LILLY FORSCHUNG GMBH[ELIL]

PRIORITY-DATA: 1999GB-014222 (June 18, 1999)

PATENT-FAMILY:

PUB-NO	PUB-DATE	LANGUAGE
GB 2351081 A	December 20, 2000	EN
WO 0078726 A1	December 28, 2000	EN
AU 200057228 A	January 9, 2001	EN

DESIGNATED-STATES: AE AG AL AM AT AU AZ BA BB BG BR BY CA CH CN CR CU CZ DE DK DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE SG SI SK SL TJ T M TR TT TZ UA UG US UZ VN YU ZA ZW AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TZ UG ZW

APPLICATION-DATA:

PUB-NO	APPL-DESCRIPTOR	APPL-NO	APPL-DATE
GB 2351081A	N/A	1999GB-014222	June 18, 1999
AU 200057228A	N/A	2000AU-057228	June 19, 2000
WO2000078726A1	Based on	2000WO-US11881	June 19, 2000

INT-CL-CURRENT:

TYPE	IPC DATE
CIPS	A61P3/00 20060101
CIPS	A61P5/50 20060101
CIPS	C07D233/22 20060101
CIPS	C07D405/10 20060101
CIPS	C07D409/10 20060101
CIPS	C07D409/14 20060101

ABSTRACTED-PUB-NO: GB 2351081 A

BASIC-ABSTRACT:

NOVELTY - Dihydroimidazole, dihydro-oxazole and dihydrothiazole derivatives (I) are new.

DESCRIPTION - Dihydroimidazole, dihydro-oxazole and dihydrothiazole derivatives of formula (I) and their salts and esters are new.

R1-R3, R9 = H or 1-8C alkyl; or

R1+R3, together with the carbon atoms to which they are attached = 3-7C carbocycle or a bond; or

CR1R2 or CR3R9 = 3-7C spirocarbocycle;

X = O, S or NR5;

R5 = H, 1-8C alkyl, optionally substituted aryl or an amino protecting group;

n = 0-2;

R4 = substituted phenyl or formula (a);

Y1 = O(CH2)k, (CH2)kO, CO, CHOH, CONR, NRCO, NR'CONR'', (CH2)kW1(CH2)b (optionally substituted by alkyl or OH), ethynylene-(CH2)k, (CH2)k-ethynylene, CH=CH(CH2)k, (CH2)kCH=CH, NR'''', SO2, SO2NR'', NR'''SO2 or a bond;

b, k = 0-4, provided that b+k at most 4;

W1 = O, S, SO, SO2, SO2NR'', NR''SO2, NR'', CONR', NR'CO, CH=CH, ethynylene, CO, NR''''CONR'''' or a bond;

R, R', R'', R''' = H, 1-4C alkyl or benzyl;

R'''' = H, 1-8C alkyl, benzyl or an amino protecting group;

R6 = phenyl, naphthyl, heteroaryl or 4,5-dihydroisoxazolinyl (all optionally substituted);

R7 = H, 1-8C alkyl, 1-8C alkoxy, 3-7C cycloalkyl, 3-7C cycloalkyl(1-8C alkoxy), OH, halogen, carbo(1-8C alkoxy), 1-6C haloalkyl, 1-8C haloalkoxy, (tetrahydropyran-2-yl)methoxy, S(O)m(1-8C alkyl), Z2(CH2)qZ1(CH2)pCH3, Z2(CH2)q'Z3 or optionally substituted phenyl(1-8C alkyl), phenoxy, phenyl(1-8C alkoxy), naphthyl, heteroaryl or S(O)m(1-8C alkyl)aryl;

R8 = H, 1-8C alkyl, 1-8C alkoxy, 3-7C cycloalkyl, 3-7C cycloalkyl(1-8C alkoxy), OH, halogen, carbo(1-8C alkoxy), 1-6C haloalkyl, 1-8C haloalkoxy or optionally substituted phenyl(1-8C alkyl);

Z1, Z2 = O, S, SO, SO2, sulfoximino, NR13 or a bond;

Z3 = optionally protected OH or SH, NR14R15 or protected amino;

R13-R15 = H, 1-8C alkyl, optionally substituted aryl(1-8C alkyl) or optionally substituted phenyl; or

NR14R15 = heterocyclic ring containing 2-6C (optionally substituted and/or with one C replaced by O or S);

p = 0-4;

q, q' = 1-5;

m, m' = 0-2;

provided that, when X = NH and Y1 is a bond, R is not 1-phenyl-1-cyclohexylmethyl or phenyl optionally substituted by halo, 1-6C alkylthio, 1-6C alkyl, CF3, phenyl, acylamino, aminosulfonyl, methoxy, indol-5-yl, 1-phenyl-1-cyclohexylmethyl or 1-6C alkylaminosulfonyl.

None given.

USE - For treatment of diabetes, diabetic complications, metabolic disorders and related diseases where impaired glucose disposal is present (claimed) such as cardiovascular disease and post operative insulin resistance induced by anesthesia. (I) may also be used as research tools.

ADVANTAGE - (I) potentiate insulin secretion under high glucose conditions and have no effect in low glucose conditions.

BTC6,F7 cells were grown to confluence and incubated with glucose and (I) for 1 hour. Insulin content of the supernatant was measured by

radioimmunoassay, giving EC50 for (I) of less than 10 mM.

EQUIVALENT-ABSTRACTS:

ORGANIC CHEMISTRY

Preparation: (I) may be prepared by reaction of bromo-substituted 2-hydroxybenzaldehyde with 3-cyano-alpha-bromobenzene in the presence of 2 equivalents of sodium methoxide to give the benzofuran derivative of formula (II). This is then reacted with EDAOTs (not defined) to replace the cyano with dihydroimidazole giving the precursor (III), which is finally reacted with arylic boronic acid by Suzuki coupling to give (I').

Ar is not defined.

Preferred Definitions:

R1, R2 = H;

R3, R9 = H or methyl;

R6 = aryl(1-8C alkyl), naphthyl or optionally substituted heteroaryl.

Dosage is 0.05-20 (0.1-5) mg/kg/day. Administration is oral, rectal, transdermal, subcutaneous, topical, intravenous, intramuscular or nasal.

5-Bromo-2-(2-methoxyethoxy)phenyl-4,5-dihydro-1H-imidazole (0.4 g) was dissolved in 1,4-dioxan (20 ml) and tetrakis(triphenylphosphine palladium (0.115 g) and 2M sodium carbonate (2 ml) added under argon. 5-Chloro-2-thiophenboronic acid (0.244 g) was added and the solution heated at 80 degrees C for 18 hours and then cooled to room temperature. The resulting solid was filtered off, the solution acidified with 2N hydrochloric acid, evaporated in vacuo and chromatographed on silica gel using dichloromethane and methanol (90:10) as the eluant, giving 5-(3-chloro-2-fluorophenyl)-2-(2-methoxyethoxy)phenyl-4,5-dihydro-1H-imid zole (0.16 g, 36% yield, m.pt. 204-206 degrees C).

TITLE-TERMS: NEW OXAZOLE DERIVATIVE USEFUL TREAT DIABETES COMPLICATED METABOLISM DISORDER DISEASE IMPAIR GLUCOSE DISPOSABLE PRESENT

DERWENT-CLASS: B03

CPI-CODES: B06-H; B07-D09; B07-E01; B07-F01; B14-F01; B14-F02; B14-F09; B14-F10; B14-S04;

CHEMICAL-CODES: Chemical Indexing M2 *01* Fragmentation Code M1 M111 M113 M280 M320 M413 M510 M521 M532 M540 M710 P520 P522 P816 Specific Compounds RA3141 Registry Numbers 346638

Chemical Indexing M2 *02* Fragmentation Code F012 F014 F017 F610 G010 G013 G100 M1 M111 M113 M210 M211 M240 M282 M320 M413 M510 M521 M532 M540 M710 P520 P522 P816 Specific Compounds RA316F Registry Numbers 346720

Chemical Indexing M2 *03* Fragmentation Code F012 F522 G011 G013 G100 H4 H401 H481 H8 M1 M111 M113 M280 M311 M321 M342 M373 M391 M413 M510 M521 M532 M540 M710 P520 P522 P816 Specific Compounds RA316G Registry Numbers 346721

Chemical Indexing M2 *04* Fragmentation Code F012 F522 G013 G019 G100 K0 L1 L143 M1 M111 M113 M280 M320 M413 M510 M521 M532 M540 M710 P520 P522 P816 Specific Compounds RA316K Registry Numbers 346725

Chemical Indexing M2 *05* Fragmentation

Code F011 F012 F421 F522 G013 G100 H1 H141 H2 H201 M1 M113 M280 M320 M413 M510 M522 M531 M540 M710 P520 P522 P816 Specific Compounds RA316L Registry Numbers 346726

Chemical Indexing M2 *06* Fragmentation Code F012 F522 G013 G015 G100 H6 H602 H608 H642 M1 M111 M113 M280 M320 M413 M510 M521 M532 M540 M710 P520 P522 P816 Specific Compounds RA316M Registry Numbers 346727

Chemical Indexing M2 *07* Fragmentation Code F012 F019 F211 F522 G013 G100 M1 M113 M119 M280 M320 M413 M510 M522 M531 M540 M710 P520 P522 P816 Specific Compounds RA316N Registry Numbers 346728

Chemical Indexing M2 *08* Fragmentation Code D012 D100 F012 F522 G013 G100 M1 M113 M119 M280 M320 M412 M511 M521 M531 M540 M710 P520 P522 P816 Specific Compounds RA316O Registry Numbers 346729

Chemical Indexing M2 *09* Fragmentation Code F012 F522 G013 G020 G111 G221 M1 M112 M113 M280 M320 M413 M510 M521 M532 M540 M710 P520 P522 P816 Specific Compounds RA316P Registry Numbers 346730

Chemical Indexing M2 *10* Fragmentation Code F012 F522 G011 G013 G100 H7 H721 M1 M111 M113 M210 M214 M231 M240 M281 M320 M413 M510 M521 M532 M540 M710 P520 P522 P816 Specific Compounds RA316Q

Registry Numbers 346731

Chemical Indexing M2 *11* Fragmentation Code D012 D022 D100 F012 F522 G011 G013 G100 H5 H541 H8 M1 M112 M113 M119 M210 M211 M272 M281 M320 M412 M511 M521 M532 M540 M710 P520 P522 P816 Specific Compounds RA316R Registry Numbers 346732

Chemical Indexing M2 *12* Fragmentation Code F012 F013 F015 F522 F620 G010 G013 G100 M1 M113 M119 M280 M320 M413 M510 M522 M532 M540 M710 P520 P522 P816 Specific Compounds RA316S Registry Numbers 346733

Chemical Indexing M2 *13* Fragmentation Code D012 D790 F012 F522 G013 G100 M1 M113 M119 M280 M320 M412 M511 M521 M531 M540 M710 P520 P522 P816 Ring Index Numbers 01197 Specific Compounds RA316T Registry Numbers 346734

Chemical Indexing M2 *14* Fragmentation Code D012 E720 F012 F522 G013 G100 M1 M113 M119 M280 M320 M412 M511 M521 M531 M540 M710 P520 P522 P816 Ring Index Numbers 00904 Specific Compounds RA316U Registry Numbers 346735

Chemical Indexing M2 *15* Fragmentation Code D012 D022 D100 F012 F522 G011 G020 G111 G221 M1 M113 M114 M119 M280 M320 M412 M511 M521 M532 M540 M710 P520 P522 P816 Specific Compounds RA316V Registry Numbers 346736

Chemical Indexing M2 *16* Fragmentation Code D012 D022 E530 F012 F522 G013 G100 H6 H602 H641 M1 M113 M119 M280 M320 M412 M511 M521 M531 M540 M710 P520 P522 P816 Ring Index Numbers 40806 Specific Compounds RA316W Registry Numbers 346737

Chemical Indexing M2 *17* Fragmentation Code D012 D300 F012 F522 G011 G100 M1 M113 M119 M280 M320 M412 M511 M521 M531 M540 M710 P520 P522 P816 Specific Compounds RA316X Registry Numbers 346738

Chemical Indexing M2 *18* Fragmentation Code F012 F522 G011 G013 G100 H7 H731 M1 M113 M121 M133 M210 M211 M240 M281 M312 M321 M332 M342 M413 M510 M521 M532 M540 M710 P520 P522 P816 Specific Compounds RA316Y Registry Numbers 346739

Chemical Indexing M2 *19* Fragmentation Code M281 M320 M413 M510 M521 M532 M540 M710 P520 P522 P816 Specific Compounds RA316Z Registry Numbers 346740

Chemical Indexing M2 *20* Fragmentation Code F012 F522 G010 G015 G100 H6 H601 H641 J0 J011 J3 J331 M1 M113 M121 M136 M280 M320 M413 M510 M521 M532 M540 M710 P520 P522 P816 Specific Compounds RA3170 Registry Numbers 346741

Chemical Indexing M2 *21* Fragmentation Code C316 F012 F522 G010 G013 G100 K0 K4 K442 M1 M113 M121 M142 M280 M320 M413 M510 M521 M532 M540 M710 P520 P522 P816 Specific Compounds RA3171

Registry Numbers 346742

Chemical Indexing M2 *22* Fragmentation Code D012 D220 F012 F522 G011 G100 M1 M113 M119 M280 M320 M412 M511 M521 M531 M540 M710 P520 P522 P816 Ring Index Numbers 03014 Specific Compounds RA3172 Registry Numbers 346743

Chemical Indexing M2 *23* Fragmentation Code F012 F522 G013 G014 G100 H5 H542 H581 H8 M1 M111 M113 M210 M211 M272 M282 M312 M321 M332 M342 M383 M391 M413 M510 M521 M532 M540 M710 P520 P522 P816 Specific Compounds RA3173 Registry Numbers 346744

Chemical Indexing M2 *24* Fragmentation Code C216 C316 D012 D013 D019 D030 D040 D712 D790 D799 E400 E460 E499 E600 E690 E699 F010 F011 F012 F013 F014 F015 F017 F019 F020 F021 F022 F029 F522 F599 F610 F620 F699 F710 F799 G001 G002 G010 G011 G012 G013 G014 G015 G016 G017 G019 G020 G021 G022 G029 G030 G039 G040 G050 G052 G100 G111 G112 G113 G221 G299 G530 G543 G553 G563 G573 H100 H102 H103 H121 H122 H141 H142 H143 H181 H182 H183 H201 H211 H401 H402 H441 H481 H482 H498 H521 H522 H541 H542 H543 H581 H582 H592 H594 H598 H599 H600 H641 H681 H682 H683 H721 H731 J011 J012 J013 J171 J311 J312 J321 J322 J331 J332 J341 J371 J581 J582 K330 K353 K399 K442 K499 L432 L640 L650 L660 L941 L943 M1 M111 M112 M113 M119 M121 M122 M123 M129 M131 M132 M133 M135 M136 M137 M139 M141 M142 M143 M147 M149 M150 M210 M211

M212 M213 M214 M215 M216 M220 M221 M222 M223 M224 M225 M231 M232 M233 M240 M271 M272 M273 M280 M281 M282 M283 M311 M312 M313 M314 M315 M316 M320 M321 M322 M323 M331 M332 M333 M334 M340 M342 M343 M344 M349 M353 M362 M372 M373 M381 M383 M391 M392 M393 M412 M413 M510 M513 M521 M522 M523 M531 M532 M533 M540 M541 M543 M630 M640 M650 M710 P520 P522 P816 Ring Index Numbers 00687 00895 00899 00912 01128 01404 01407 01408 41095 51957 56494 56506 56511 Markush Compounds 003033001

Chemical Indexing M2 *25* Fragmentation Code C216 C316 D012 D019 D030 D040 D712 D790 D799 F010 F012 F013 F014 F015 F017 F019 F020 F021 F022 F029 F522 F599 F620 F699 G001 G002 G010 G011 G012 G013 G014 G015 G016 G017 G019 G020 G021 G022 G029 G030 G039 G040 G050 G052 G100 G111 G112 G113 G221 G299 G530 G543 G553 G563 G573 H100 H102 H103 H121 H122 H141 H142 H143 H181 H182 H401 H402 H441 H481 H482 H498 H521 H522 H541 H542 H543 H581 H582 H592 H594 H598 H599 H600 H641 H681 H682 H683 H721 H731 J011 J012 J013 J171 J311 J312 J321 J322 J331 J332 J341 J371 J581 J582 K330 K353 K399 K442 K499 L432 L640 L650 L660 L941 L943 M1 M111 M112 M113 M119 M121 M122 M123 M129 M131 M132 M133 M135 M136 M137 M139 M141 M142 M143 M147 M149 M150 M210 M211 M212 M213 M214 M215 M216 M220 M221 M222 M223 M224 M225 M231 M232 M233 M240 M271 M272 M273 M280 M281 M282 M283 M311 M312 M313 M314 M315 M316 M320 M321 M322 M323 M331 M332 M333 M334 M340 M342 M343 M344

M349 M353 M362 M372 M373 M381 M383
M391 M392 M393 M412 M413 M510 M513
M521 M522 M523 M531 M532 M533 M540
M541 M543 M630 M640 M650 M710 P520
P522 P816 Ring Index Numbers 00688 00783
00784 00948 00951 01216 01413 01414 55208
Markush Compounds 003033002

SECONDARY-ACC-NO:

CPI Secondary Accession Numbers: 2001-014613